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OCULAR BLOOD FLOW IN PROLIFERATIVE DIABETIC RETINOPATHY PATIENT'S VS NON-PROLIFERATIVE DIABETIC RETINOPATHY- A COMPARISON STUDY.

Dr. Karen Josephine Rayen[1*], Dr. Sheela M[2], Dr. Prof. K Kanmani[3], Dr. Ajay A[4], Dr. Atchaya Sivanandam[5]

[1*]PG at Department of Ophthalmology, ACS Medical College and Hospital, Chennai Email id- karenjo1995@gmail.com
[2]Senior resident at Department of Ophthalmology, ACS Medical College and Hospital, Chennai Email id- Sheelakunaravel28@gmail.com
[3]Professor and HOD at Department of Ophthalmology, ACS Medical College and Hospital, Chennai Email id – mani.lbbo@gmail.com
[4]PG at Department of Radiology, ACS Medical College and Hospital, Chennai Email id – ajayabraham2222@gmail.com
[5]PG at Department of Ophthalmology, ACS Medical College and Hospital, Chennai Email id – atchaya1996@gmail.com

***Corresponding Author:** Dr. Karen Josephine Rayen
*Department of Ophthalmology, ACS Medical College and Hospital, Chennai Email: karenjo1995@gmail.com

ABSTRACT:

BACKGROUND: Diabetic retinopathy (DR) is a leading cause of vision impairment worldwide, characterized by changes in ocular blood flow that, progress from non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR). In the field of ophthalmology, these hemodynamic changes are crucial for early diagnosis and therapeutic interventions. In this background, the present study aims to compare ocular blood flow parameters in patients with PDR and NPDR to identify significant differences that may contribute to disease progression.

METHODOLOGY: In the present study, we received ethical and scientific approval before commencing data collection. Patients visiting ophthalmology outpatient services were screened, and those meeting the inclusion criteria provided informed consent. This prospective study included three groups;10 patients with proliferative diabetic retinopathy (PDR), 10 with non-proliferative diabetic retinopathy (NPDR), and 10 healthy controls. Ocular blood flow velocities in the ophthalmic artery, short posterior ciliary artery, central retinal vessels, and vortex veins were measured, including systolic, end-diastolic, and mean arterial velocities. Each assessment was completed in a single session of 45–60 minutes, confirming strict confidentiality. This data was analyzed using the Statistical Package for Social Studies (SPSS).

RESULTS: In the study of ocular blood flow in diabetic retinopathy, participants with PDR had an average age of 53.27 ± 10.35 years, while those with NPDR averaged 55.18 ± 12.47 years. In the study of maximum diastolic blood flow velocity, patients with PDR exhibited significantly lower velocities compared to those with NPDR in several vessels.

CONCLUSION: Retinal blood flow is significantly altered in diabetic retinopathy, with PDR patients exhibiting reduced velocities in key ocular vessels compared to NPDR, representing impaired

circulation. These findings highlighted the role of hemodynamic changes in the progression of diabetic retinopathy and suggest that assessing ocular blood flow may aid in early detection and targeted interventions to prevent vision loss in diabetic patients.

KEYWORDS: Diabetic Retinopathy, Proliferative Diabetic Retinopathy, Non-Proliferative Diabetic Retinopathy, Ocular Blood Flow, Color Doppler Imaging.

INTRODUCTION:

Diabetic retinopathy (DR) is a significant public health challenge and a leading cause of blindness globally, particularly in the United States. (1) Chronic hyperglycemia adversely affects the microvasculature, leading to focal ischemia that is critical for disease progression. (2) DR presents with various ocular changes, including microaneurysms, retinal hemorrhages, hard exudates, cotton-wool spots, venous alterations, and neovascularization in the retina. (3) The rising incidence of diabetes mellitus underscores the urgent need to address DR, especially in developed nations. (4) In India, the prevalence of DR is approximately 12.5%, with about 4% classified as vision-threatening diabetic retinopathy (VTDR). (5) Worldwide, around 27.0% of individuals with diabetes are affected by DR, contributing to an estimated 0.4 million cases of blindness. (5) Pooled analyses indicate a prevalence of 31.6% in Africa and 19.48% in Ethiopia. (6) The International Diabetes Federation reported that, as of 2019, the global prevalence of diabetic retinopathy exceeded 25%, highlighting the substantial burden it poses within the diabetic population. (7)

DR is classified into five stages:

a) No apparent retinopathy,
b) Mild non-proliferative diabetic retinopathy (M-NPDR),
c) Moderate NPDR, d) Severe NPDR (s-NPDR), and
d) Proliferative diabetic retinopathy (PDR). (8)

As a metabolic disorder linked to hyperglycemia, DR promotes the synthesis and accumulation of basement membrane components, leading to thickening of retinal blood vessel membranes and worsening microvascular complications. (9) The progression from NPDR to PDR is marked by significant changes in ocular blood flow, which is vital for managing the disease. (10) In NPDR, microaneurysms, dot-and-blot hemorrhages, and cotton wool spots reflect increased retinal permeability and capillary obstruction. (11) As DR advances to PDR, neovascularization occurs, leading to complications such as vitreous hemorrhage and tractional retinal detachment, which significantly contribute to visual loss. (12) The Early Treatment Diabetic Retinopathy Study (ETDRS) classifies NPDR into stages based on observable changes, emphasizing the need for early detection. (13) Additionally, diabetic macular edema, arising from disruption of the blood-retinal barrier, is a primary cause of vision loss. (9)

Understanding ocular blood flow differences between NPDR and PDR is crucial for effective management of diabetic retinopathy. (14) The wall-to-lumen ratio (WLR) serves as an important in vivo parameter for assessing arterial remodeling, indicating vascular stenosis and potential end-organ damage. (15) An increase in WLR suggests arterial remodeling due to wall thickening, luminal narrowing, or both. Technologies such as adaptive optics (AO) facilitate non-invasive, high-resolution imaging of retinal vessels for detailed analysis of wall thickness and WLR. (16) Although methods like laser Doppler velocimetry and video fluorescein angiography have been employed to assess hemodynamics, they are less suitable for large-scale trials. (17) Laser speckle flowgraphy (LSFG) provides a rapid, non-invasive means to quantitatively measure relative blood flow in the choroid and optic nerve head, showing strong correlation with actual blood flow measurements. This makes LSFG an effective tool for evaluating and comparing retinal blood flow in larger populations. (18)

To the best our knowledge, few studies have investigated ocular blood flow differences between patients with PDR and NPDR. Thus, this study aims to measure changes in blood flow velocity in key ocular vessels—the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries (PCA)—using color Doppler imaging. By comparing these hemodynamic alterations in individuals with DR to healthy controls, we aim to enhance our understanding of the vascular changes associated with different stages of the disease and their implications for ocular health.

MATERIAL AND METHOD:

This cross-sectional study aimed to assess changes in blood flow velocity in the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries (PCA) in patients with diabetic retinopathy (DR) using color Doppler imaging, comparing results with healthy controls. Additionally, the study explored the potential of ocular blood flow velocity as a guide for treatment decisions and a tool for monitoring intervention efficacy in DR, while also investigating its relationship with DR severity to establish a biomarker for disease progression.

Conducted at the Department of Ophthalmology, ACS Medical College and Hospital, convenience sampling was used to determine the sample size, including consecutive out-patients meeting specific inclusion and exclusion criteria. Inclusion criteria involved patients diagnosed with proliferative or non-proliferative diabetic retinopathy confirmed by fundus examination, aged above 18 years, of either gender, who consented to participate and had controlled systemic conditions. Exclusion criteria encompassed those with other ocular conditions such as retinal detachment or recent cataract surgery, a history of trauma, use of systemic steroids, age below 18 years, or significant blood disorders or anemia.

Data collection and study tools: -

The study was conducted over a year for data collection, followed by an additional year for statistical analysis and report preparation. Sociodemographic and clinical variables were recorded using a standardized proforma. Clinical assessments included Snellen's visual acuity charts and blood pressure monitoring, along with fundus examinations to confirm diabetic retinopathy. Data analysis was performed using software tools such as SPSS, R, or Stata to compare blood flow velocities between patients with proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) and to assess correlations with clinical parameters.

Methodology: -

The proposal was submitted to the Institutional Ethics Committee and the Institutional Scientific Committee for ethical and scientific clearance. Following approval, permission to commence data collection was obtained from the relevant authorities. Patients attending the ophthalmology outpatient services were screened, and those meeting the specified inclusion and exclusion criteria and providing informed consent were enrolled in the study.

This prospective study compared blood flow velocities in specific ocular vessels—including the ophthalmic artery, short posterior ciliary artery, central retinal vessels, and vortex veins—across three groups: 10 patients with proliferative diabetic retinopathy (PDR), 10 with non-proliferative diabetic retinopathy (NPDR), and 10 healthy controls. For each participant, systolic, end-diastolic, and mean arterial velocities were meticulously measured in the aforementioned vessels. The entire assessment process was designed to be completed within a single sitting, lasting approximately 45 to 60 minutes per patient. Confidentiality of all participants was strictly maintained, and study subjects were not required to disclose their names on the data collection proforma.

Statistical analysis: -

The collected data was analyzed using the Statistical Package for Social Studies (SPSS). A Chi-Square Independence test was employed to determine whether two categorical variables were related within the study population. A t-test was used to compare the means between two groups, and Pearson's correlation coefficient measured the statistical relationship or association between two continuous variables.

RESULTS:

Table-1: Demographic characteristics in the study group

Variables	Proliferative diabetic retinopathy (n=15)		Non-proliferative diabetic retinopathy (n=15)	
Age	53.27 ± 10.35		55.18 ± 12.47	
Gender				
Male	7	46.67%	6	40.00%
Female	8	53.33%	9	60.66%
Insulin dependent				
Insulin	10	66.67%	-	
non-insulin dependent	5	33.33%	-	

In the study of ocular blood flow in diabetic retinopathy, participants with PDR had an average age of 53.27 ± 10.35 years, while those with NPDR averaged 55.18 ± 12.47 years. In the PDR group, 46.67% were male and 53.33% female, whereas the NPDR group comprised 40.00% male and 60.66% female. Additionally, 66.67% of PDR patients were insulin-dependent, with none in the NPDR group.

Table-2: Clinical characteristics in the study group

Clinical characteristics	Proliferative diabetic retinopathy (n=15)	Non-proliferative diabetic retinopathy (n=15)
Systolic blood pressure	126.30 ± 17.19	118.74 ± 15..39
Diastolic blood pressure	79.56 ± 14.89	77.67 ± 11.16
HbA1C (mg/dL)	7.8 ± 1.3	-
Intraocular pressure	17.36 ± 3.14	15.26 ± 2.19

In the study of clinical characteristics, patients with PDR had a systolic blood pressure of 126.30 ± 17.19 mmHg and diastolic blood pressure of 79.56 ± 14.89 mmHg, with an average HbA1C of 7.8 ± 1.3 mg/dL. In comparison, NPDR patients had lower systolic pressure at 118.74 ± 15.39 mmHg and diastolic pressure of 77.67 ± 11.16 mmHg. The intraocular pressure was also higher in PDR patients (17.36 ± 3.14 mmHg) compared to NPDR patients (15.26 ± 2.19 mmHg).

Table-3: Maximum systolic blood flow velocity in proliferative diabetic retinopathy patient (n=15) and non-proliferative diabetic retinopathy (n=15)

Vessels	Proliferative diabetic retinopathy	Non-proliferative diabetic retinopathy	P-value
OA (ophthalmic artery)	30.25 ± 6.74	37.29 ± 6.69	0.007
PCA (posterior ciliary arteries)	14.11 ± 2.05	15.86 ± 2.31	0.036
CRA (central retinal artery)	10.35 ± 2.43	13.79 ± 3.11	0.002
CVR (central retinal vein)	5.66 ± 1.97	4.51 ± 0.69	0.04
VV (Vortex Veins)	5.12 ± 1.5	5.54 ± 1.1	0.62

In the study, patients with proliferative diabetic retinopathy (PDR) had significantly lower maximum systolic blood flow velocities than those with non-proliferative diabetic retinopathy (NPDR) in several vessels. The ophthalmic artery velocities were 30.25 ± 6.74 cm/s for PDR and 37.29 ± 6.69

cm/s for NPDR (p = 0.007). For the posterior ciliary arteries, PDR was 14.11 ± 2.05 cm/s versus 15.86 ± 2.31 cm/s for NPDR (p = 0.036). The central retinal artery showed PDR at 10.35 ± 2.43 cm/s compared to NPDR at 13.79 ± 3.11 cm/s (p = 0.002). In the central retinal vein, PDR recorded 5.66 ± 1.97 cm/s, while NPDR had 4.51 ± 0.69 cm/s (p = 0.04). No significant difference was found in the vortex veins, with PDR at 5.12 ± 1.5 cm/s and NPDR at 5.54 ± 1.1 cm/s (p = 0.62).

Table-4: Maximum diastolic blood flow velocity in proliferative diabetic retinopathy patient (n=15) and non-proliferative diabetic retinopathy (n=15)

Vessels	Proliferative diabetic retinopathy	Non-proliferative diabetic retinopathy	P-value
OA (ophthalmic artery)	6.31 ± 2.87	11.22 ± 4.09	0.0007
PCA (posterior ciliary arteries)	4.17 ± 0.81	5.54 ± 2.27	0.0001
CRA (central retinal artery)	3.75 ± 0.77	4.51 ± 0.74	0.01
CVR (central retinal vein)	3.01 ± 0.58	2.78 ± 0.61	0.29
VV (Vortex Veins)	3.12 ± 0.65	3.87 ± 1.1	0.03

In the study of maximum diastolic blood flow velocity, patients with proliferative diabetic retinopathy (PDR) exhibited significantly lower velocities compared to those with non-proliferative diabetic retinopathy (NPDR) in several vessels. The ophthalmic artery (OA) recorded 6.31 ± 2.87 cm/s for PDR versus 11.22 ± 4.09 cm/s for NPDR (p = 0.0007). In the posterior ciliary arteries (PCA), PDR had 4.17 ± 0.81 cm/s compared to 5.54 ± 2.27 cm/s for NPDR (p = 0.0001). The central retinal artery (CRA) showed PDR at 3.75 ± 0.77 cm/s and NPDR at 4.51 ± 0.74 cm/s (p = 0.01). No significant difference was found in the central retinal vein (CVR), with PDR at 3.01 ± 0.58 cm/s and NPDR at 2.78 ± 0.61 cm/s (p = 0.29).

Table-5: Mean arterial blood flow velocities in proliferative diabetic retinopathy patient (n=15) and non-proliferative diabetic retinopathy (n=15)

Vessels	Proliferative diabetic retinopathy	Non-proliferative diabetic retinopathy	P-value
OA (ophthalmic artery)	17.12 ± 5.78	24.15 ± 8.12	0.018
PCA (posterior ciliary arteries)	8.32 ± 1.48	10.87 ± 3.20	0.009
CRA (central retinal artery)	6.10 ± 1.23	8.21 ± 2.30	0.004

In the analysis of mean arterial blood flow velocities, patients with proliferative diabetic retinopathy (PDR) had significantly lower velocities compared to those with non-proliferative diabetic retinopathy (NPDR). For the ophthalmic artery (OA), PDR patients exhibited a velocity of 17.12 ± 5.78 cm/s, while NPDR patients had a higher velocity of 24.15 ± 8.12 cm/s (p = 0.018). In the posterior ciliary arteries (PCA), PDR showed 8.32 ± 1.48 cm/s versus 10.87 ± 3.20 cm/s for NPDR (p = 0.009). The central retinal artery (CRA) also demonstrated lower velocities in PDR at 6.10 ± 1.23 cm/s compared to 8.21 ± 2.30 cm/s in NPDR (p = 0.004).

DISCUSSION:

Diabetic retinopathy (DR) is a leading complication of diabetes, affecting over 130 million people globally, and is a key indicator of systemic microvascular issues in diabetes. Accurate prevalence data on both PDR and NPDR forms in T2DM is essential for guiding public health efforts, improving clinical management, and supporting targeted interventions to slow the progression of diabetic complications.

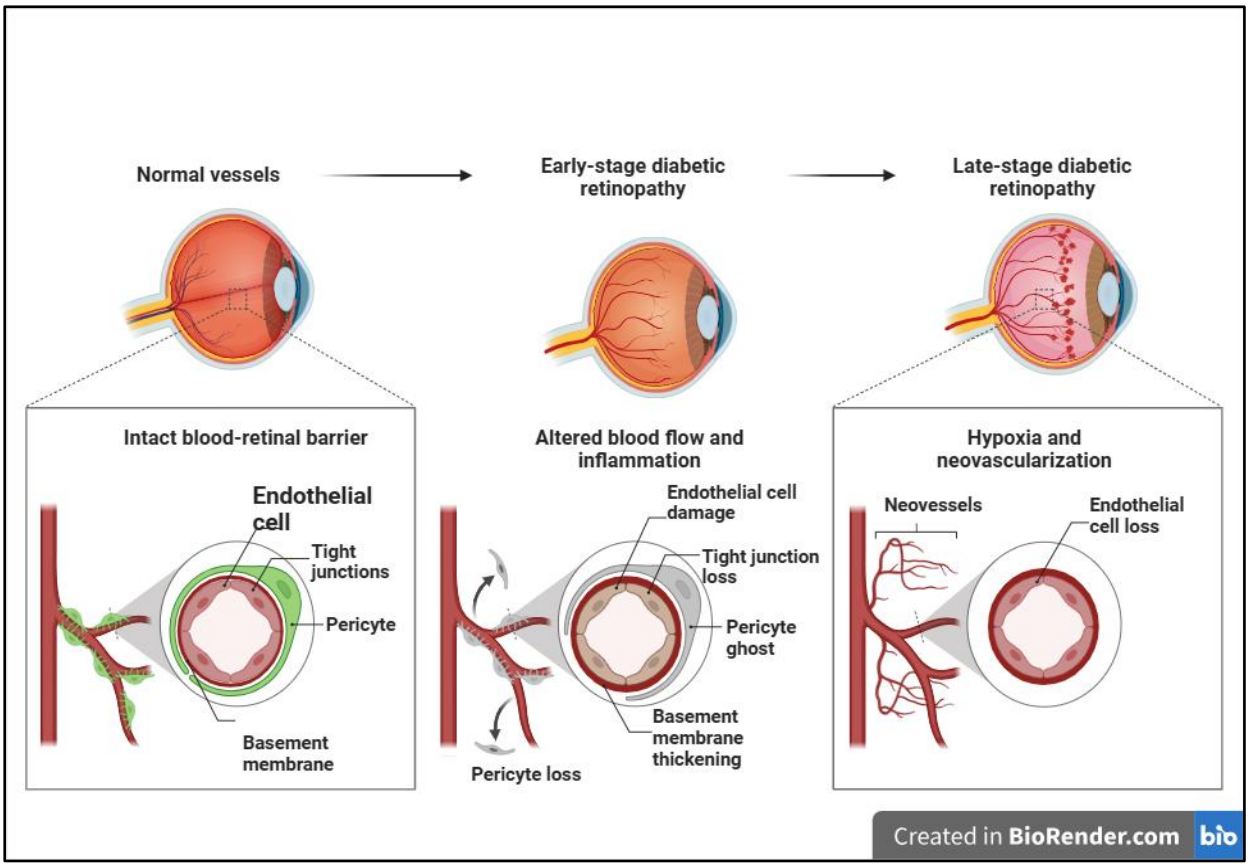

Figure no 1: - Pathological vascular changes in DR.

Color Doppler imaging has revolutionized the ability to assess orbital blood flow by providing real-time visualization of blood flow dynamics under physiological conditions. This non-invasive technique allows for detailed examination of the vascular structures in the eye and orbit, enabling clinicians to evaluate blood flow velocities and patterns with high accuracy, offering valuable insights into ocular health and any potential circulatory abnormalities.

In the study by **Yoshitaka Ueno et al.**, a control group of 24 individuals had a mean age of 67.2 ± 10.1 years, with a male-to-female ratio of 11:13. Among 47 patients with no diabetic retinopathy (NDR), the mean age was 62.7 ± 12.9 years, male-to-female ratio was 27:20, and HbA1c was 7.0 ± 0.9%, with an average diabetes duration of 10.1 ± 6.9 years. This NDR group also showed systolic blood pressure of 134.6 ± 16.5 mmHg, diastolic blood pressure of 126.6 ± 17.5 mmHg, intraocular pressure of 13.0 ± 2.5 mmHg, ocular perfusion pressure of 51.3 ± 7.2 mmHg, total cholesterol of 202.0 ± 35.6 mg/dL, and low-density lipoprotein of 102.2 ± 27.9 mg/dL; hypertension was present in 46.8% and dyslipidemia in 31.9%. In a separate analysis by **V. Patel,** 24 non-diabetic controls and 76 diabetic patients (63 insulin-dependent, 13 non-insulin-dependent) were evaluated. In the present study, the PDR group had a mean age of 53.27 ± 10.35 years, with 46.67% males, while the NPDR group's mean age was 55.18 ± 12.47 years, with 40% males; additionally, 66.67% of PDR patients were insulin-dependent, unlike the NPDR group.

This analysis highlights that advanced DR, especially in insulin-dependent patients, is associated with increased systemic and ocular health risks, including higher HbA1c, blood pressure, and duration of diabetes.

In **A. Mendívil's et al.**, demostration, PDR patients exhibited significantly lower systolic and diastolic blood flow velocities in the ophthalmic artery (OA) and central retinal artery (CRA) compared to healthy controls ($p < 0.01$ and $p < 0.001$, respectively). Similarly, in the present study, PDR patients had lower velocities than NPDR in vessels like the OA and posterior ciliary artery (PCA), indicating impaired ocular blood flow. **Kohner et al**. reported normal ocular blood flow in

severe retinopathy, while **Grunwald et al.** found reduced arterial and venous velocities in retinopathy, though total blood flow remained unchanged without photocoagulation.
Zvia Burgansky-Eliash et al. noted slower arterial velocities in diabetics compared to controls (3.74 ± 1.09 mm/s vs. 4.19 ± 0.99 mm/s) and lower venous velocities (2.61 ± 0.65 mm/s vs. 3.03 ± 0.59 mm/s). **V. Patel et al.** observed higher retinal blood flow in untreated diabetic retinopathy, which decreased after pan-retinal photocoagulation. In our study, PDR patients had significantly lower velocities than NPDR in the OA (17.12 ± 5.78 cm/s vs. 24.15 ± 8.12 cm/s, p = 0.018), PCA (8.32 ± 1.48 cm/s vs. 10.87 ± 3.20 cm/s, p = 0.009), and CRA (6.10 ± 1.23 cm/s vs. 8.21 ± 2.30 cm/s, p = 0.004).
This study reinforces the significant ocular blood flow abnormalities observed in DR, particularly in PDR. PDR patients exhibited significantly reduced blood flow velocities in key vessels like the ophthalmic artery (OA), posterior ciliary artery (PCA), and central retinal artery (CRA) compared to NPDR patients, highlighting compromised ocular circulation.

CONCLUSION

Retinal blood flow is significantly increased in DR compared to non-diabetic controls and diabetic patients without retinopathy, likely as a compensatory response to retinal ischemia. This study highlights significant ocular blood flow abnormalities in diabetic retinopathy, with PDR patients showing notably reduced velocities in key vessels such as the OA, PCA, and CRA compared to NPDR patients, indicating impaired ocular circulation.

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