OCULAR DUPLEX DOPPLER SONOGRAPHY AND ITS ROLE ~~IN~~ IN EARLY DIAGNOSIS OF DIABETIC RETINOPATHY

ABSTRACT:

Diabetic retinopathy is the most common cause of vision loss among people with diabetes and a leading cause of blindness among working-age adults in India. It is a form of microangiopathy, and is the most common ocular complication seen in diabetic patients. Diabetic retinopathy progresses from non proliferative to proliferative retinopathy. The non proliferative retinopathy is the milder form and it is reversible. As the progression to proliferative retinopathy happens, the patients are symptomatic and become irreversible. Vascular changes and subsequent ocular hemodynamic changes are critical events in the pathogenesis of diabetic retinopathy. Colour doppler imaging is one of the most widely used and well-established techniques for assessing ocular blood flow velocities in the retro bulbar vessels. This is a non-invasive, painless imaging method with highly reproducibility. Estimation of orbital blood flow velocity from colour doppler imaging of the ophthalmic artery and central retinal artery is a technique offering great potential for the identification of early retinopathy in diabetic patients.

KEYWORDS: Diabetic retinopathy, non-proliferative retinopathy, proliferative retinopathy, Colo~~u~~r doppler imaging, orbital blood flow velocity, ophthalmic artery, central retinal artery, ophthalmoscopy, ocular doppler,

ABBREVIATIONS: PI - Pulsatility index, RI – Resistive index, PSV – Peak systolic velocity, EDV – End diastolic velocity, NPDR – Non proliferative diabetic retinopathy, PDR - Proliferative diabetic retinopathy

INTRODUCTION

Diabetic retinopathy is the most common cause of vision loss among people with diabetes and a leading cause of blindness among working-age adults in India. It is a form of microangiopathy, and is the most common ocular complication seen in diabetic patients[2].

The early stages of diabetic retinopathy usually have no symptoms. Diabetic retinopathy generally appears after several years of diabetes over an average of 5–10 years; often it goes unnoticed until vision loss occurs[3-6]. Early detection, timely treatment, and appropriate follow-up care of diabetic eye disease can protect against vision loss.

Diabetic retinopathy progresses from non proliferative to proliferative retinopathy. The non proliferative retinopathy is the milder form and it is reversible. As the progression to proliferative retinopathy happens, the patients are symptomatic and become irreversible[7].

Vascular changes and subsequent ocular hemodynamic changes are critical events in the pathogenesis of diabetic retinopathy.

Prevention of diabetic retinopathy is by regular examinations, treatment and control of blood sugar levels. With strict ~~glycemic~~glycaemic control there is good chance for prevention of diabetic retinopathy. The tertiary or last stage of treatment is surgical laser photocoagulation, which is recommended for significant macular edema in high risk proliferative diabetic ~~retinopathy .~~retinopathy. This laser therapy is used to seal the leaking blood vessels, reduce retinal oxygen demand and remove if there is presence of haemorrhage in vitreous by vitrectomy.

There are also newer developments in treating retinopathy by use of anti-vascular endothelial growth factors, useful in treating both macular edema and proliferative retinopathy.

Colour doppler imaging is one of the most widely used and well-established techniques for assessing ocular blood flow velocities in the retro bulbar vessels. This is a non-invasive, painless imaging method with highly reproducibility.

Estimation of orbital blood flow velocity from colour doppler imaging of the ophthalmic artery and central retinal artery is a technique offering great potential for the identification of early retinopathy in diabetic patients.

AIMS AND OBJECTIVES

1. The aim of this study is to evaluate hemodynamic changes of ophthalmic artery and central retinal artery.

2. To compare the hemodynamic changes of ophthalmic artery and central retinal artery in diabetic patients with non proliferative retinopathy and controls.

3. To compare the hemodynamic changes of ophthalmic artery and central retinal artery in diabetic patients with proliferative retinopathy and controls.

4. To compare the hemodynamic changes of ophthalmic artery and central retinal artery in diabetic patients with non proliferative retinopathy and patients with proliferative retinopathy.

MATERIALS AND METHODS

Patients with T2DM presenting to Medical College and Hospital were included in this cross sectional study. An institutional review board clearance was obtained. A written informed voluntary consent was obtained from all the study subjects.

A total of 15 non diabetic healthy volunteers (30 eyes) were assessed to interpret the normal ocular hemodynamic values and fundal examinations of the eyes were done.

A further random 50 eyes of 25 diabetic patients with and without visual complaints will be studied to assess the ocular hemodynamic changes in Doppler and fundal examination of the eyes is done for classification of the retinopathy if any. Both the eyes are taken for the study, thus accounting for 50 numbers of pathological cases. The total number of examined eye is 80.

Inclusion criteria

- Patients having normal blood glucose and normal blood pressure levels volunteering for the study.
- Diabetic patients with duration of disease from 2-15 years.
- Diabetic patients without manifestations of diabetic retinopathy.
- Both sexes were included in the study

Exclusion criteria

- Cataract
- Glaucoma
- Hypertension
- Juvenile diabetes
- Previous history of eye trauma or surgery
- Total or partial blindness
- Pregnancy induced diabetes mellitus

Male and female patients with diabetes for more than 2 years and after being clinically evaluated were included in the study. The patients were referred from department of medicine of our hospital for Doppler evaluation and sent to department of ophthalmology for fundal study.

The sensitivity, range of curve, specificity, positive predictive value and negative predictive value were calculated.

Statistics: Percentage analysis, Chi Square test, ANOVA.

OCULAR DOPPLER:

An informed consent was obtained prior to the study after explaining the procedure of the examination to the patient. The examinations were carried out in a Philips affinity USG machine. The patient was asked lie down in supine position on the examination bed.

To perform the ultrasound measurement of OA and CRA, transducer with frequency range of 5-10 MHz was used for this study. A blob of gel was applied to the closed eyelid, and the probe was positioned gently with minimal pressure. The ophthalmic artery was identified as a large calibre vessel adjacent to the optic nerve and adjacent small calibre laterally placed vessel was the central retinal.

Pulsed doppler spectral analysis of the ophthalmic artery and central retinal artery allows the determination of peak systolic velocity and end-diastolic velocity.

Indices of Measurement:

(1) Resistance index

(2) Pulsatility index

(3) Peak systolic velocity

(4) End diastolic velocity

Resistive Index is not altered by the angle of doppler since it is a ratio, but V_{max} & V_{min} are altered by the angle of doppler. Resistive index is a useful measure to study the difference between various groups of patients & also avoid any interobserver bias.

The resistive index and pulsatility index are classical indices of vascular resistance. They were calculated as follows:

Resistive index (RI) = (PSV-EDV) / PSV (peak systolic velocity - end diastolic velocity) / peak systolic velocity

Pulsatility index (PI) = (PSV - EDV) / TAV (peak systolic velocity - end diastolic velocity) / time averaged velocity

FUNDAL EXAMINATION:

For the fundal examination, the pupil of the eye was first dilated. Tropicamide drops (30%) were used for dilatation and after 30 minutes the fundal study was carried out. The eyes were examined in a split lamp using 90 dioptre lens and fundus for examined for macular edema /~~hemorrhage~~haemorrhage / microaneurysms / cotton wool spots/ exudates / venous beading/ neovascularisation or all of the above. After examination the retinopathy was classifies as either non proliferative type of proliferative type.

After documentation of the hemodynamics and the fundal imaging, a conclusion was made with the help of statistical analyses.

IMAGES

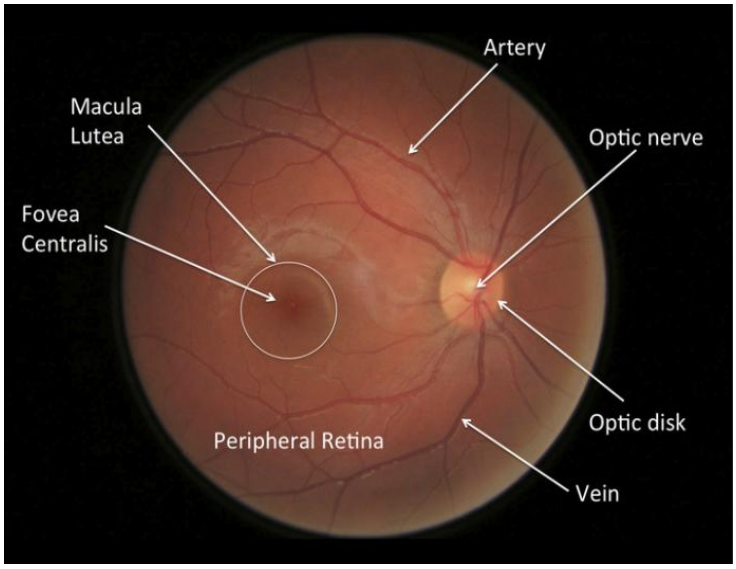

FIG 1:NORMAL FUNDAL IMAGE OF EYE

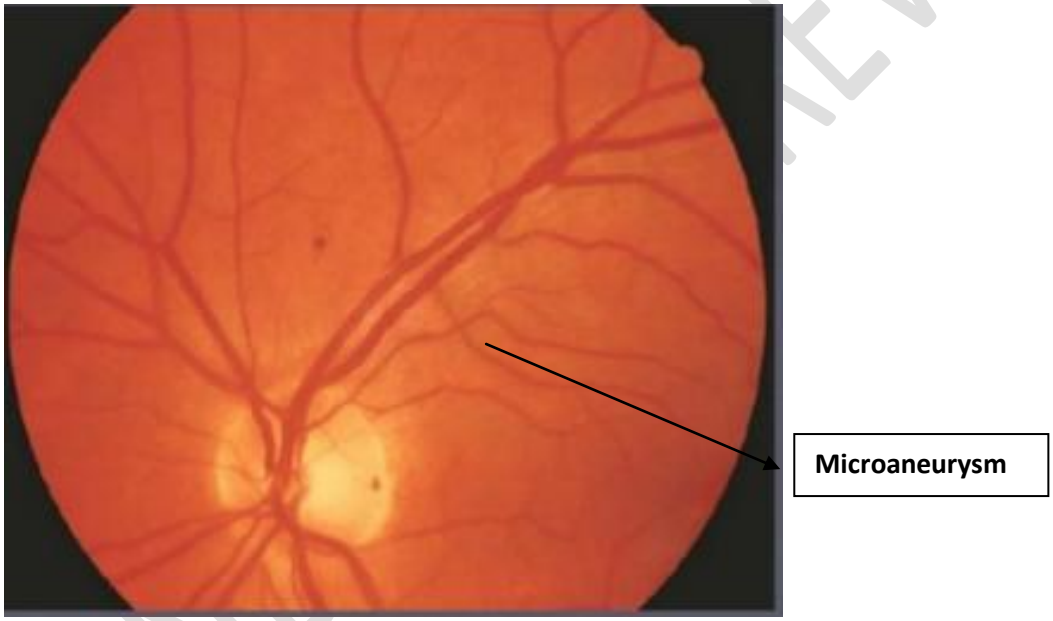

FIG 2:MICROANEURYSM IN EARLY NON PROLIFERATIVE RETINOPATHY

FIG 3:EXUDATES IN NON PROLIFERATIVE RETINOPATHY
A - Hard exudates
B – Soft exudates or cotton wool exudates

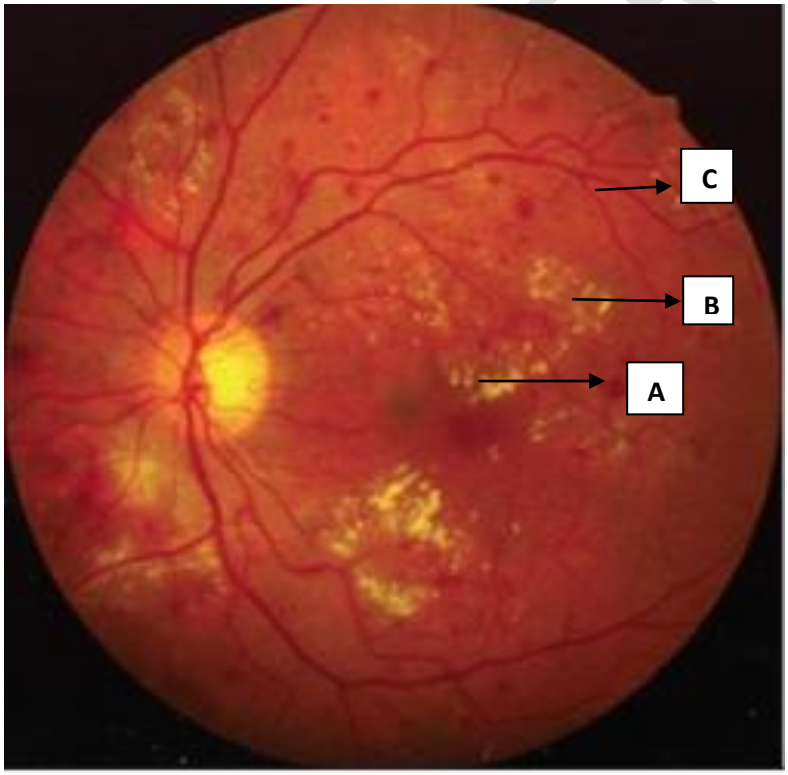

FIG 4:MACULAR EDEMA WITH EXUDATES AND HEMORRHAGE IN NOPROLIFERATIVE DIABETIC RETINOPATHY
A - Macular edema
B – Hard exudates
C – Micro hemorrhages

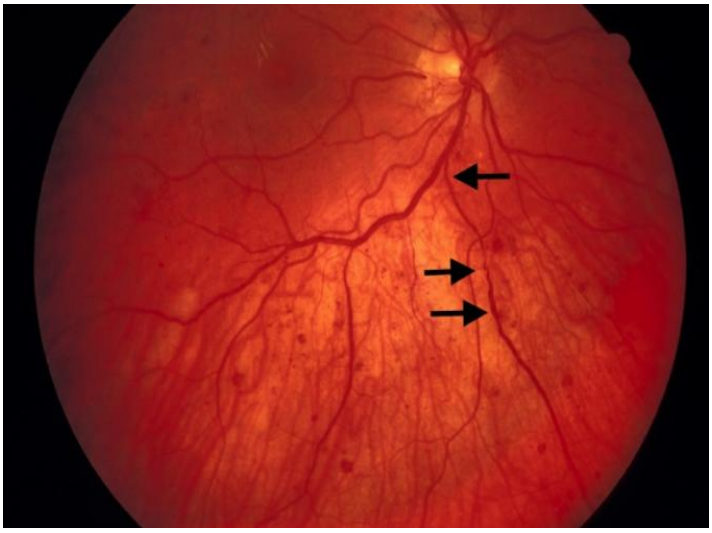

FIG 5:VENOUS BEADING IN SEVERE NON PROLIFERATIVE DIABETIC RETINOPATHY

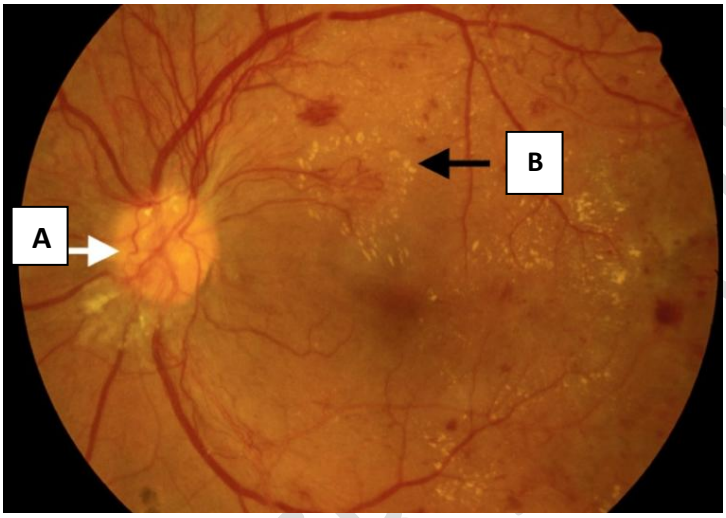

FIG 6:PROLIFERTATIVE DIABETIC RETINOPATHY
A – Neovascularization overlying the optic disc
B – Hard exudates

<u>TRANSPALPEBRAL ULTRASOUND – COLOUR DOPPLER IMAGING OF OCULAR VESSELS IN A NORMAL SUBJECT</u>

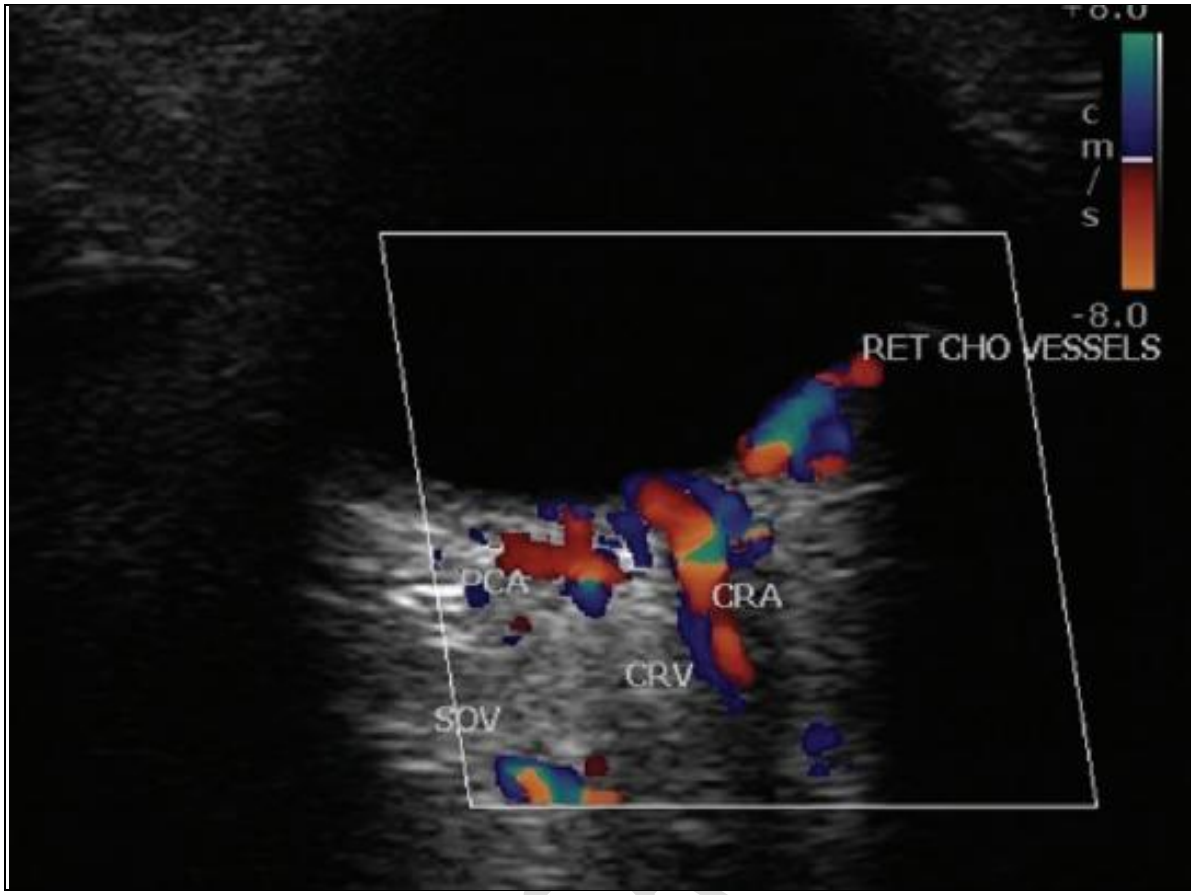

FIG 7:ANATOMIC LOCATION OF OCULAR VESSELS IN A NORMAL SUBJECT
(CRA: central retinal artery, PCA: posterior ciliary artery, CRV: Central retinal vein, SOV: Superior ophthalmic vein)

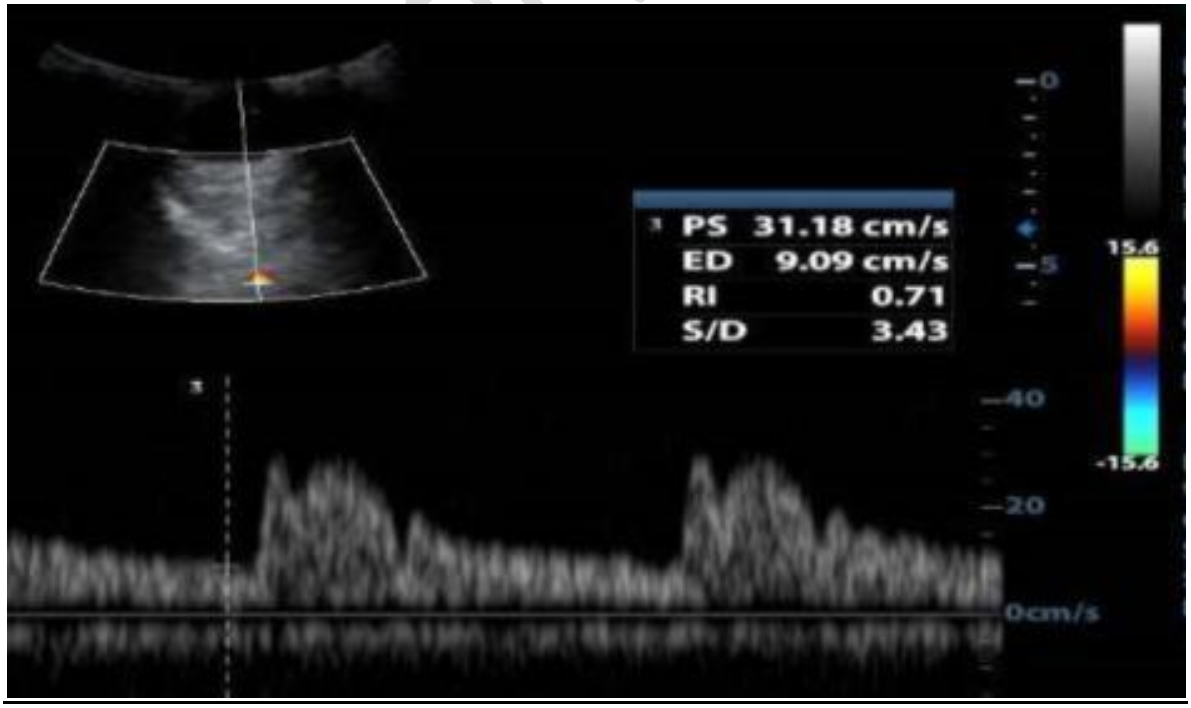

FIG 8:OPHTHALMIC ARTERY - NORMAL

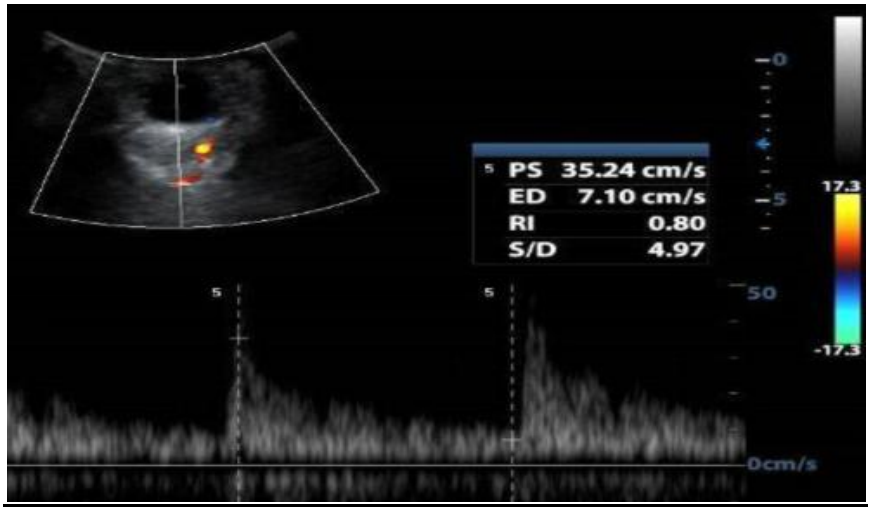

FIG 9:OPHTHALMIC ARTERY – DIABETIC RETINOPATHY

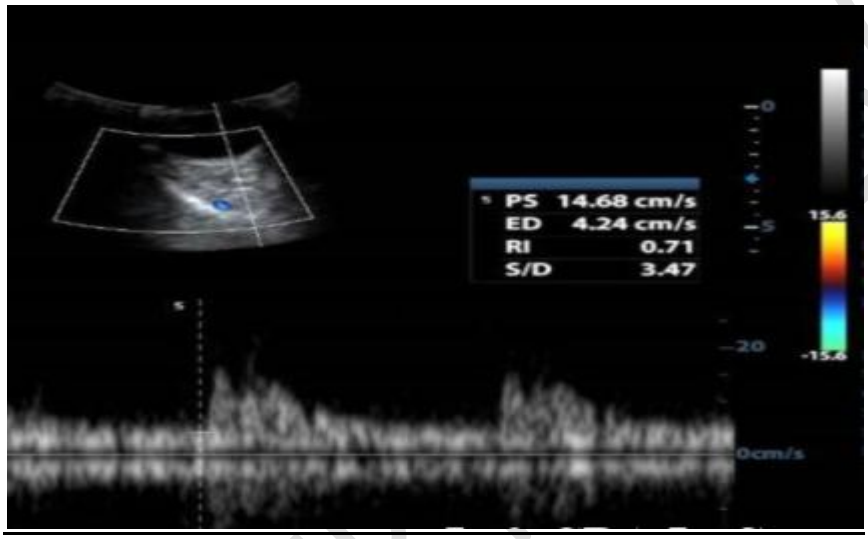

FIG 10:CENTRAL RETINAL ARTERY - NORMAL

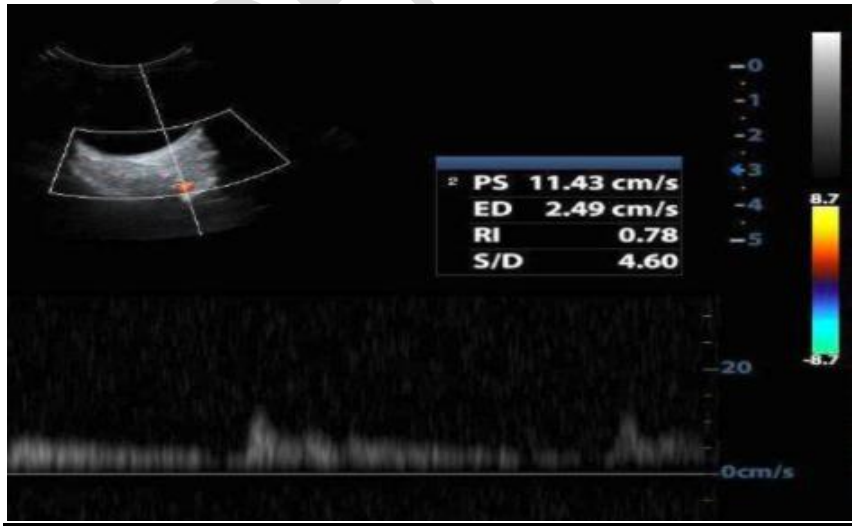

FIG 11:CENTRAL RETINAL ARTERY – DIABETIC RETINOPATHY

OBSERVATIONS AND RESULTS:

Table 1: Age Distribution

Age in years	No. of Cases	Percentage
30-50 years	12	24%
>50 years	38	76%
Total	50	100%

The majority of patients were more than >50 years (76%). 24% of patients were between 30-50 years old.

Table 2: Sex Distribution

Sex	No. of Cases	Percentage
Male	30	60%
Female	20	40%
Total	50	100%

The maximum numbers of patients were males (60%). 40% of patients were females.

Table 3: Duration of Diabetes

Duration of Diabetes	No. of Cases	Percentage
<10 years	24	48%
>=10 years	26	52%
Total	50	100%

In our study, 52% of patients had diabetes more than 10 years and 48% of patients had diabetes less than 10 years.

Table 4: Visual Complaints

Visual Complaints	No. of Cases	Percentage
Yes	24	48%
No	26	52%
Total	50	100%

48% of patients had visual complaints and 52% of patients didn't have visual complaints.

Table 5: Examined Side

Examined Side	No. of Cases	Percentage
Left	25	50%
Right	25	50%
Total	50	100%

Half of the patients were examined on left side and other half of the patients were examined on right side.

Table 6: Fundoscopy Result

Fundoscopy	No. of Cases	Percentage
Normal	2	4%
Non proliferative retinopathy	36	72%
Proliferative retinopathy	12	24%
Total	50	100%

The result shows that majority of patients were non proliferative (72%). 4% of diabetic patients were normal and 24% of patients were proliferative.

Fig. 12 : Fundoscopy Result

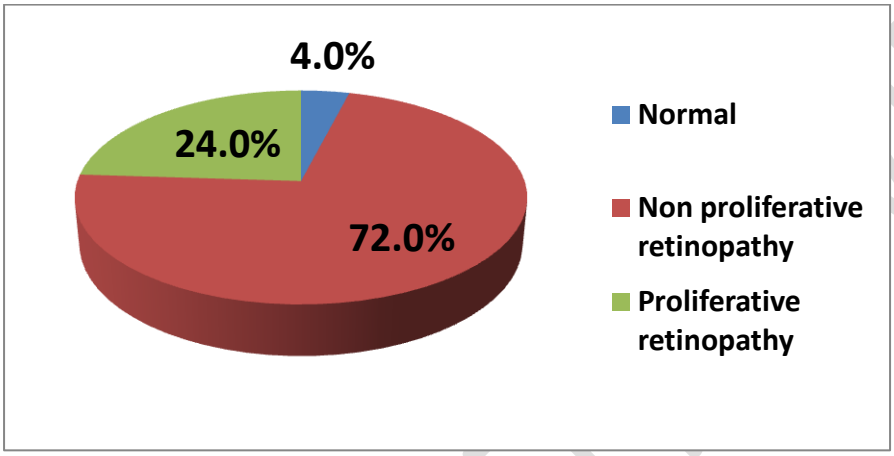

Table 7: Comparison of clinical parameters between ophthalmic artery and central retinal artery groups

Clinical Parameters		Mean±SD	't' value	P value
Peak systolic velocity (cm/sec)	Ophthalmic Artery	33.3394±0.7686	210.619	<0.001*
	Central Retinal Artery	11.8042±0.4698		
End diastolic velocity (cm/sec)	Ophthalmic Artery	6.4762±0.5927	37.023	<0.001
	Central Retinal Artery	3.3602±0.1871		
Resistivity index	Ophthalmic Artery	0.8055±0.0197	28.744	<0.001*
	Central Retinal Artery	0.71±0.019		
Pulsatility index	Ophthalmic Artery	1.7525±0.0904	30.781	<0.001*
	Central Retinal Artery	1.3738±0.0701		

***-Significant**

The paired 't' test result showed that peak systolic velocity, end diastolic velocity, resistivity index and pulsatility index values were significantly lower in central retinal artery group when comparing to ophthalmic artery group (p<0.001*).

Table 8: Correlation between age and fundoscopy results of patients with diabetes

			Fundoscopy			Total
			Normal	Non proliferative retinopathy	Proliferative retinopathy	
Age in years	30-50 years	Count	0	10	2	12
		% within Age in years	0.0%	83.3%	16.7%	100.0%
	>50 years	Count	2	26	10	38
		% within Age in years	5.3%	68.4%	26.3%	100.0%
Total		Count	2	36	12	50
		% within Age in years	4.0%	72.0%	24.0%	100.0%

Chi-Square Value = 1.267 P value = 0.531 Not Significant

The chi-square test shows that there is no significant correlation between age in years and fundoscopy results in patients with diabetes (p=0.531). The inference is that age does not affect the progress of retinopathy.

Table 9: Correlation between sex and fundoscopy results of patients with diabetes

			Fundoscopy			Total
			Normal	Non proliferative retinopathy	Proliferative retinopathy	
Sex	Male	Count	2	21	7	30
		% within Sex	6.7%	70.0%	23.3%	100.0%
	Female	Count	0	15	5	20
		% within Sex	0.0%	75.0%	25.0%	100.0%
Total		Count	2	36	12	50
		% within Sex	4.0%	72.0%	24.0%	100.0%

Chi-Square Value = 1.389 P value = 0.499 Not Significant

The chi-square test shows that there is no significant correlation between sex and fundoscopy in patients with diabetes (p=0.499). Sex does not play a role in severity or progression of retinopathy.

Table 10: Correlation between examined side and fundoscopy results of patients with diabetes

			Fundoscopy			Total
			Normal	Non proliferative retinopathy	Proliferative retinopathy	
Examined Side	Left	Count	1	19	5	25
		% within Examined Side	4.0%	76.0%	20.0%	100.0%
	Right	Count	1	17	7	25
		% within Examined Side	4.0%	68.0%	28.0%	100.0%
Total		Count	2	36	12	50
		% within Examined Side	4.0%	72.0%	24.0%	100.0%

Chi-Square Value = 0.444 P value = 0.801 Not Significant

The chi-square test shows that there is no significant correlation between examined side and fundoscopy in patients with diabetes (p=0.801).

Table 11: Mean and SD of clinical parameters with respect to fundoscopy results in patients with diabetes

OPHTHALMIC ARTERY		n	Mean	Std. Deviation	Std. Error
Peak systolic velocity (cm/sec)	Normal	2	34.8200	0.42426	0.30000
	Non proliferative retinopathy	36	32.1064	0.58479	0.09746
	Proliferative retinopathy	12	31.1250	0.79215	0.22867
	Total	50	33.3394	0.76867	0.10871
End diastolic velocity (cm/sec)	Normal	2	7.0750	0.26163	0.18500
	Non proliferative retinopathy	36	6.5964	0.60357	0.10060
	Proliferative retinopathy	12	6.0158	0.23608	0.06815
	Total	50	6.4762	0.59268	0.08382
Resistive index	Normal	2	0.784361	0.0107592	0.0076079
	Non proliferative retinopathy	36	0.800678	0.0188383	0.0031397
	Proliferative retinopathy	12	0.823594	0.0087210	0.0025175
	Total	50	0.805525	0.0197086	0.0027872
Pulsatility index	Normal	2	1.653464	0.0477967	0.0337974
	Non proliferative retinopathy	36	1.729528	0.0846688	0.0141115
	Proliferative retinopathy	12	1.838115	0.0437201	0.0126209
	Total	50	1.752546	0.0904402	0.0127902

The hemodynamic values of ophthalmic artery are obtained. The above table shows that the peak systolic velocity and pulsatility index resistive index are increased in retinopathy. The mean cut off value of resistive index in proliferative diabetic retinopathy being more than 0.82. There is decrease in end diastolic velocity and peak systolic velocity, normal end diastolic velocity being 7cm/sec, non proliferative retinopathy is 6.5cm/sec and proliferative diabetic retinopathy being 6cm/sec.

Table 12: Association between ophthalmic artery clinical parameters and fundoscopy result in patients with diabetes

OPTHALMIC ARTERY		Sum of Squares	DF	Mean Square	F	Sig.
Peak systolic velocity (cm/sec)	Between Groups	9.900	2	4.950	12.212	0.000*
	Within Groups	19.052	47	0.405		
	Total	28.952	49			
End diastolic velocity (cm/sec)	Between Groups	3.780	2	1.890	6.614	0.003*
	Within Groups	13.432	47	0.286		
	Total	17.212	49			
Resistive index	Between Groups	0.006	2	0.003	9.945	0.000*
	Within Groups	0.013	47	0.000		
	Total	0.019	49			
Pulsatility index	Between Groups	0.127	2	0.063	10.847	0.000*
	Within Groups	0.274	47	0.006		
	Total	0.401	49			

***-Significant**

Between groups- between diabetic and non diabetic patients

Within groups – between non proliferative and proliferative diabetic retinopathy

The ANOVA test results shows that there is a significant difference in mean values of ophthalmic artery with respect to the fundoscopy results in patients with diabetes ($p<0.001$*). There is evidence of mean increase in pulsatility index and resistive index of ophthalmic artery and decrease in end diastolic velocity and peak systolic velocity.

Table 13: Mean and SD of clinical parameters with respect to fundoscopy results in patients with diabetes

CENTRAL RETINAL ARTERY		n	Mean	Std. Deviation	Std. Error
PSV (cm/sec)	Normal	2	12.3800	0.09899	0.07000
	Non proliferative retinopathy	36	11.6675	0.40005	0.06668
	Proliferative Retinopathy	12	11.2017	0.30337	0.08758
	Total	50	11.8042	0.46982	0.06644
EDV (cm/sec)	Normal	2	3.3250	0.02121	0.01500
	Non proliferative retinopathy	36	3.2239	0.17508	0.02918
	Proliferative retinopathy	12	3.1750	0.08660	0.02500
	Total	50	3.3602	0.18713	0.02646
Resistive index	Normal	2	.70	0.000	0.000
	Non proliferative retinopathy	36	.710	0.013	0.002
	Proliferative retinopathy	12	.720	0.024	0.007
	Total	50	.715	0.019	0.003
Pulsatility index	Normal	2	1.336916	0.0160558	0.0113532
	Non proliferative retinopathy	36	1.342211	0.0426490	0.0071082
	Proliferative retinopathy	12	1.475052	0.0372234	0.0107455
	Total	50	1.373881	0.0701062	0.0099145

The hemodynamic values of central retinal artery are obtained. The hemodynamic changes were similar to that of ophthalmic artery in retinopathy. The peak systolic velocity and pulsatility index resistive index are increased in retinopathy. The mean cut off value of resistive index in proliferative diabetic retinopathy being more than 0.72, where the normal is 0.7 and non proliferative retinopathy showed mean value of 0.71. There is decrease in end diastolic velocity and peak systolic velocity, normal end diastolic velocity being 3.3cm/sec, non proliferative retinopathy is 3.2cm/sec and proliferative diabetic retinopathy being 3.1cm/sec.

Table 14: Association between central retinal artery clinical parameters and fundoscopy result in patients with diabetes

CENTRAL RETINAL ARTERY		Sum of Squares	df	Mean Square	F	Sig.
PSV (cm/sec)	Between Groups	4.192	2	2.096	14.873	0.000*
	Within Groups	6.624	47	0.141		
	Total	10.816	49			
EDV (cm/sec)	Between Groups	0.560	2	0.280	11.388	0.000*
	Within Groups	1.156	47	0.025		
	Total	1.716	49			
Resistive index	Between Groups	0.005	2	0.002	9.107	0.000*
	Within Groups	0.013	47	0.000		
	Total	0.017	49			
Pulsatility index	Between Groups	0.162	2	0.081	47.993	0.000*
	Within Groups	0.079	47	0.002		
	Total	0.241	49			

***-Significant**

The ANOVA test results shows that there is a significant difference in mean values of central retinal artery with respect to the fundoscopy results in patients with diabetes ($p<0.001$*). There is evidence of mean increase in pulsatility index and resistive index of central retinal artery and decrease in end diastolic velocity and peak systolic velocity.

DISCUSSION:

Using colour doppler imaging, the resistive indices of orbital vessels was measured in patients with diabetes mellitus and was found to be significantly greater than those of normal subjects and to be further increased in the presence of proliferative diabetic retinopathy. The resistive index has been used as a measure of vascular resistance in the artery. The value of calculating the resistive index has previously been highlighted by Mulhernet al. (1996), helping to give a more accurate and non-angle dependent measurement. In the present study, the resistive index of patients in ophthalmic and central retinal arteries with diabetic retinopathy was significantly greater than that of normal subjects and further increased with proliferative diabetic retinopathy.

There is a significant difference in the end diastolic velocity and peak systolic velocity of ophthalmic artery and central retinal artery noted between the patients with and without diabetic retinopathy. In patients with diabetic retinopathy it is seen that both end diastolic velocity and peak systolic velocity are very much reduced and is statistically significant as well. The end diastolic velocity and peak systolic velocity of central retinal artery in patients without diabetic retinopathy are increased in comparison to patients with diabetic retinopathy. Goebel et al in his study has proved that the resistive index of ocular arteries is increased in patients with diabetes when compared to the normal individuals. This investigation is concurring with the findings.

The resistive index is increased in patients with diabetic retinopathy. Dimitrova in her work has also found the significant increase of RI in patients with diabetic retinopathy when compared to the controls.

Mendivil and Cuartero (1996) have reported colour doppler imaging findings of a mixed group of type I and type II diabetics with proliferative diabetic retinopathy after laser photocoagulation. Pan retinal photocoagulation resulted in reduction of the peak systolic velocity in ophthalmic artery when compared to

values before laser treatment. This parameter again could not be assessed in the current study as patients undergoing photocoagulation were not included in the study.

In the study conducted by Dimitrova, there was a reduction of blood flow velocity both in non proliferative and proliferative retinopathy and the increase in resistive index was evident in central retinal artery and ophthalmic artery. The finding of the present study that the RI of CRA and OA in patients with and without retinopathy are significantly greater than those of normal individuals is in agreement with certain other studies such as MacKinnon et al.

Chart 1. The cut off values between non proliferative and proliferative retinopathy are as follows:

	RESISTIVE INDEX		**PULSATALITY INDEX**	
	OA	**CRA**	**OA**	**CRA**
NORMAL	**0.78**	**0.70**	**1.6**	**1.33**
NON PROLIFERATIVE RETINOPATHY	**0.80**	**0.71**	**1.7**	**1.34**
PROLIFERATIVE RETINOPATHY	**0.82**	**0.72**	**1.8**	**1.47**

These values help in identifying the progression of diabetic retinopathy and proper life style modifications and medications can prevent the manifestation of proliferative retinopathy.

LIMITATIONS:

Certain limitations of the present study should be considered:
Firstly, sample size was relatively small. Second, the comparison of our results with relatively younger individuals. More specific age group of patients would have been helpful and more accurate. Posterior ciliary artery and superior ophthalmic vein is not studied.

Another potential limitation was operator-dependent nature of ultrasonography although it is non-invasive, easily performed, and confidential method for evaluating colour doppler imaging.
We have ruled out conditions like glaucoma and hypertension, previous intraocular surgeries which are factors in causing ocular vasculopathy.

CONCLUSION:

The aim of this study is to evaluate hemodynamic changes of ophthalmic artery and central retinal artery in diabetic patients with diabetic retinopathy by comparing it with normal individuals and to find the cut off value between the non proliferative diabetic retinopathy and proliferative diabetic retinopathy groups.

Using colour doppler imaging, blood flow velocities i.e. peak systolic velocity, end diastolic velocity, resistive index and pulsatility index were found in ophthalmic artery and central retinal artery for 80 eyes (30 controls and 50 tests). In this study, it is found that resistive index and pulsatility index is increased in both the vessels of patients with diabetic retinopathy. Peak systolic velocity and end diastolic velocity is decreased in both the orbital vessels in patients with diabetic retinopathy. Colour Doppler imaging can be used in evaluating the hemodynamic circulation in orbital vessels and is a useful modality to assess the progression of diabetic retinopathy when other techniques are inaccessible to these vessels. Measurements give reliable information on blood flow velocities at the sites of complex vasculature.

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