

# Assessment of Ocular Neurovascular Alterations in Type 2 Diabetes using High Frequency Ultrasonic Imaging and Color Doppler

Gaana A., Nitishkumar Yeslawath, Lokesh Babu, Arun Kamireddy, Abinaya Giridesh

## ABSTRACT

**Background:** Diabetes is a metabolic syndrome that is a common cause of visual disturbances including blindness. Significant number of patients with type 2 diabetes develop ocular neurovascular complications over a period. These complications can be well assessed by ultrasonic imaging coupled with color doppler. **Methods:** This hospital-based, case-control study included 50 diabetic patients using strict inclusion and exclusion criterion in addition to 50 control subjects without diabetes or any other disease known to produce ocular neurovascular changes. All patients and controls underwent B-mode ultrasonography and color doppler flow imaging to obtain peak systolic velocity (PSV), end-diastolic velocity (EDV) & resistive index (RI) from central retinal artery (CRA), posterior ciliary artery (PCA) and ophthalmic artery (OA) in addition to optic nerve and optic nerve sheath diameters (OND & ONSD). The values obtained were then analyzed using appropriate statistical tools and methods. **Results:** Variable degrees of negative correlation was noted between fundoscopic grading and OND & ONSD. Variable degree of negative correlation was achieved between PSV & EDV in OA, PCA & RA and positive correlation with RI in all the three arteries. There was significant reduction in PSV with increase in RI in diabetic patients compared to normal subjects in all the three arteries. **Conclusion:** Ocular neurovascular alterations are significant cause of morbidity in patients with type 2 diabetes. USG and color doppler can detect changes in the neural thickness and vascular parameters in early stages of disease, hence should be included in the routine ophthalmic screening protocol of diabetic patients.

## Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia occurring when the body is unable to produce adequate insulin or cannot effectively use the produced insulin. Type 2 diabetes accounts for the bulk of diabetic cases worldwide [1]. According to the 9<sup>th</sup> edition of the International Diabetes Federation (IDF) atlas, India has 2<sup>nd</sup> highest number of diabetic patients (77 million) with another 43.9 million undiagnosed cases [2]. Approximately two-third of all Type 2 diabetics are expected to develop diabetic retinopathy over a period of time [3]. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes [4]. Annual progression to sight threatening DR range from 3.4% to 12.3% [5].

Significant and quantifiable dysfunction of the retinal microvasculature commences within weeks of diabetes onset in patients characterized by changes in retinal blood flow, impaired autoregulation, and abnormal vascular permeability to plasma proteins [6]. There is evidence of decreased nerve fiber diameter and degeneration of the nerve fiber layer in diabetic retinas which is likely due to a loss of ganglion cells or ganglion cell axons [7]. Associated atrophy of retinal axons is also noted in diabetics [8].

Ultrasound is an ideal modality to assess the eye due to its superficial location and cystic composition. It is non-ionizing,

Department of Radiology, Aarupadai Veedu Medical College and Hospital, Puducherry, India

**Corresponding Author :** Dr. (Prof.) Nitishkumar Yeslawath, Head, Department of Radiodiagnosis, Aarupadai Veedu Medical College and Hospital, Puducherry, India

e-mail: drnithish@gmail.com

**Received:** 14 July 2021

**Accepted:** 22 July 2021

**How to Cite this Article:** Gaana A, Yeslawath N, Babu L, Kamireddy A, Giridesh A. Assessment of Ocular Neurovascular Alterations in Type 2 Diabetes using High Frequency Ultrasonic Imaging and Color Doppler. J Int Med Sci Acad. 2022 Jan-March;35(1): 67-72.

**Access this article online :** [www.jimsaonline.com](http://www.jimsaonline.com)



cost effective and allows real time imaging of the eye while providing detailed cross-sectional anatomy of the entire globe [9]. It can be safely performed on outdoor patients without any use of anesthetics or sedative therapy. B-scan ultrasonography is useful in diabetic patients with vitreous hemorrhage or other media opacities, where the retina cannot be visualized directly on ophthalmic examination [10]. B-scan ultrasonography can also demonstrate if retinal detachment /other pathologies are present. Changes in the vascular flow parameters can be quantitatively assessed by

doppler parameters in central retinal artery (CRA), ophthalmic artery (OA), and posterior ciliary artery (PCA). Involvement of the neuroglia can be assessed by measuring optic nerve diameter (OND) and optic nerve sheath diameter (ONSD).

### Aim

To assess the usefulness of Ultrasound (USG) and Color Doppler Imaging (CDI) as an early screening test to detect changes in the ocular neurovascular components among diabetes patients.

### Objectives

- 1) To measure blood flow velocity (Peak systolic velocity - PSV, End-diastolic velocity - EDV and resistive index - RI) in the CRA, PCA and OA in patients with type 2 diabetes using Doppler imaging and compare the results with age matched normal control subjects.
- 2) To measure Optic nerve diameter (OND) and optic nerve sheath diameter (ONSD) in the same patients with type 2 diabetes using high frequency Ultrasound imaging and compare the results with age matched normal control subjects.

### Methods

This hospital-based, case-control study that included 50 diabetic patients and 50 control subjects was performed in our institution over a period of two years following approval from institutional ethics committee and after obtaining written consent.

### Inclusion Criteria

All patients above 18 years including both sexes with type 2

diabetes referred to our department for USG and CDI.

### Exclusion Criteria

Patients with hypertension (BP >140/90), cardiac disease or any other diseases known to cause alterations in ocular hemodynamic blood flow.

All patients included in the study underwent USG & CDFI on Mindray DC-360 Color Doppler ultrasound scanner using a 5-7 Hz high frequency linear array probe. Patient was placed in supine position and examined with gentle pressure applied over the closed eye without compressing the anterior chamber. CRA was localized along the optic nerve while PCA was seen curving along the posterior surface of the eyeball. To visualize the ophthalmic artery, the probe was slightly angulated nasally. PSV, EDV & RI was measured in all the above-three vessels (Image 1).

Measurements of the OND and ONSD were taken at a distance of 3mm from the posterior surface of the eyeball (Image 2). A distance of 3 mm from the globe was chosen as an ideal location to measure ONSD based on the anatomical fact that the optic nerve sheath is normally found to be loose near the eyeball, with a much bigger space between the optic nerve and the sheath than anywhere else in its course, thus presenting bulbous form behind the eyeball [11].

The information from grey scale images, spectral waveforms and optic nerve measurements were recorded in predesigned proforma. The data was analyzed using SPSS software and p-value of <0.05 was interpreted as statistically significant.

Similar measurements were also acquired in 50 age-matched controls without diabetes, or any other disease known to

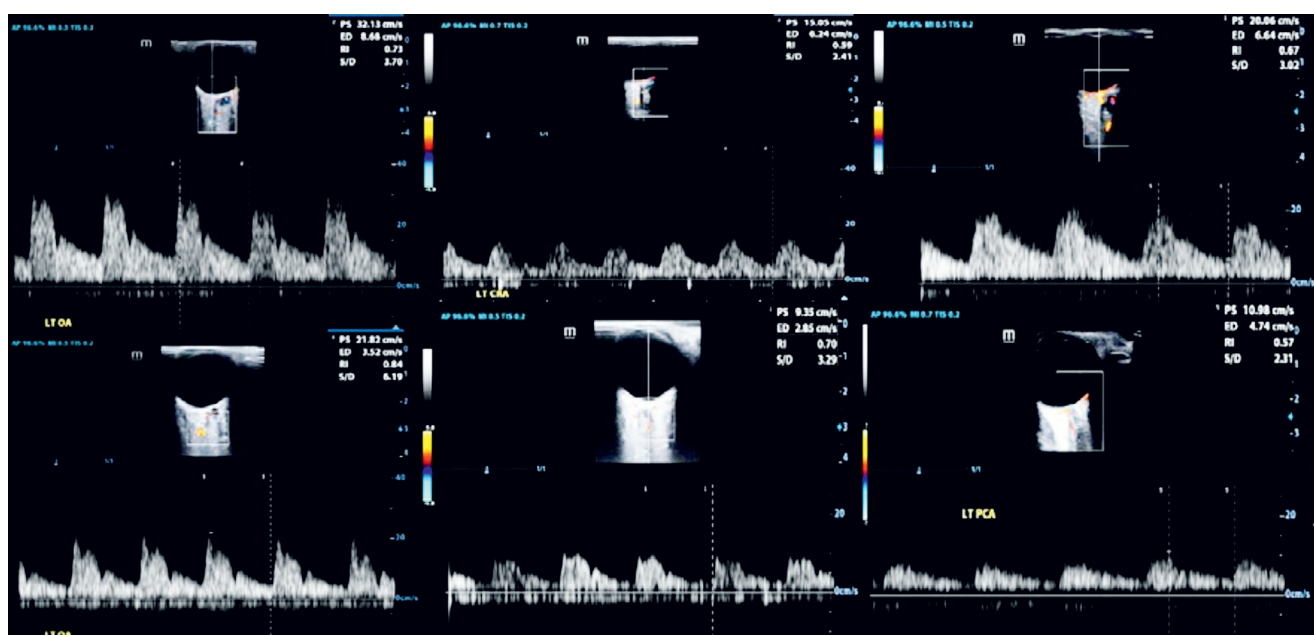


Image 1: Velocities (PSV & EDV) and RI in OA, CRA & PCA in normal subject in that order (top row) with corresponding images in diabetic subjects in that order in lower row showing decreased velocities & increased RI in the latter

cause alteration in ocular hemodynamic blood flow. Patients were divided into 2 groups based on fundoscopic findings – Non-Diabetic retinopathy and Diabetic retinopathy. Comparison of the variations in blood flow parameters and optic nerve diameters among controls and patients with no diabetic retinopathy was done using t-test. Pearson correlation coefficient values was used to find the association between fundoscopic grading and ocular neurovascular parameters.

### Observations and Results

Out of 50 diabetic patients in our study, 31 were males and 19 were females. This shows the diabetic retinopathy (DR) is more prevalent in males.

Table 1 summarizes the data from patients and controls in our study as mean  $\pm$  standard deviation (SD) for both cases [divided into no DR, mild/moderate/severe non-proliferative DR (NPDR), proliferative DR (PDR)] and controls.

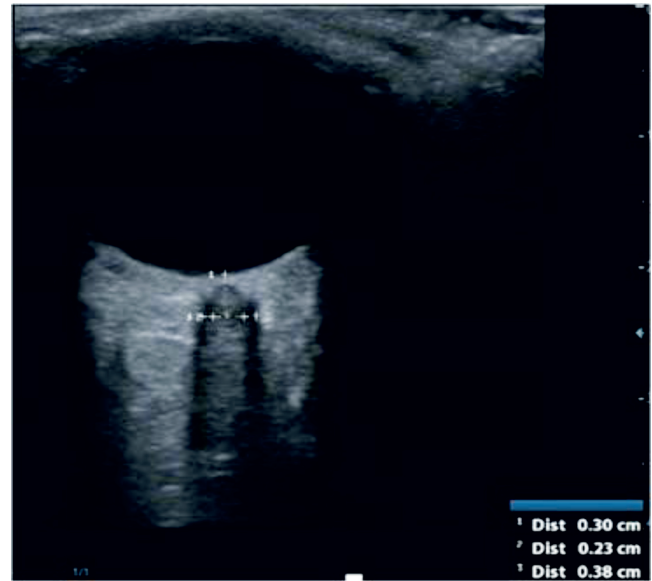


Image 2: Measurement of ONSD

Table 1: Neurovascular parameters in cases and controls

	CONTROLS	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
AGE	53 $\pm$ 15.3	43.6 $\pm$ 13.5	58.8 $\pm$ 11.2	57.5 $\pm$ 13.5	60.3 $\pm$ 12.1	59 $\pm$ 13.1
HbA1c		8.2 $\pm$ 1.1	8.5 $\pm$ 1.5	10.3 $\pm$ 1.06	9.7 $\pm$ 1.7	10.2 $\pm$ 2.05
OND	2.97 $\pm$ 0.15	2.97 $\pm$ 0.11	2.7 $\pm$ 0.14	2.5 $\pm$ 0.09	2.36 $\pm$ 0.15	2.3 $\pm$ 0.13
ONSD	4.98 $\pm$ 0.15	5.04 $\pm$ 0.12	4.87 $\pm$ 0.14	4.8 $\pm$ 0.17	4.77 $\pm$ 0.16	4.8 $\pm$ 0.17
OA-PSV	31.7 $\pm$ 1.8	30.2 $\pm$ 2.26	27.07 $\pm$ 1.56	25.8 $\pm$ 1.69	26 $\pm$ 1.5	23.47 $\pm$ 2.64
OA-EDV	8.6 $\pm$ 0.13	7.3 $\pm$ 1.12	4.9 $\pm$ 1.01	4.37 $\pm$ 2.05	3.58 $\pm$ 0.65	3 $\pm$ 0.64
OA-RI	0.73 $\pm$ 0.01	0.78 $\pm$ 0.02	0.83 $\pm$ 0.03	0.85 $\pm$ 0.02	0.87 $\pm$ 0.01	0.87 $\pm$ 0.01
CRA-PSV	11.89 $\pm$ 1.2	10.6 $\pm$ 1.12	9.19 $\pm$ 0.86	8.77 $\pm$ 0.34	8.4 $\pm$ 0.38	8.3 $\pm$ 0.68
CRA - EDV	3.92 $\pm$ 0.36	2.8 $\pm$ 0.79	2.09 $\pm$ 0.82	1.7 $\pm$ 0.37	1.47 $\pm$ 0.19	1.4 $\pm$ 0.29
CRA-RI	0.7 $\pm$ 0.01	0.76 $\pm$ 0.03	0.79 $\pm$ 0.04	0.8 $\pm$ 0.02	0.83 $\pm$ 0.02	0.85 $\pm$ 0.02
PCA-PSV	12.9 $\pm$ 1.27	11.3 $\pm$ 1.06	10.3 $\pm$ 0.5	10.6 $\pm$ 0.53	10.4 $\pm$ 0.41	9.7 $\pm$ 0.72
PCA-EDV	4.3 $\pm$ 0.59	4.5 $\pm$ 0.54	3.6 $\pm$ 0.78	3.3 $\pm$ 0.6	3.2 $\pm$ 0.3	2.9 $\pm$ 0.21
PCA-RI	0.66 $\pm$ 0.06	0.65 $\pm$ 0.01	0.66 $\pm$ 0.01	0.66 $\pm$ 0.01	0.67 $\pm$ 0.01	0.69 $\pm$ 0.01

Fundoscopy examination and grading of retinopathy revealed that 19 patients had no DR, 10 patients had mild NPDR, 8 had moderate NPDR, 6 had severe NPDR and 6 had PDR. One patient revealed nonspecific changes. Figure 1 shows the same information in form of pie-chart.

Our study revealed strong negative correlation between fundoscopic grading and OND in DR with p value of  $<0.00001$  and moderate negative correlation between fundoscopic grading and ONSD in DR with p value of 0.000024.

There was a moderate negative correlation between fundoscopic grading and OA PSV & EDV in DR with p value of  $<0.00001$ . There was a statistically significant reduction in OA PSV values in cases when compared to controls ( $t =$

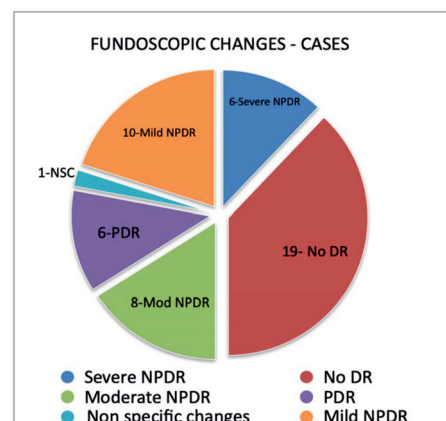


Figure 1: Pie-Chart showing distribution of patients based on fundoscopic grading of DR

7.8927;  $p < 0.00001$ ) while there was a significant increase in OA RI in diabetic patients when compared with normal control subjects ( $t = 15.6545$ ;  $p < 0.00001$ ). also, there was a strong positive correlation between fundoscopic grading and OA RI value in DR with  $p$  value of  $< 0.00001$ .

There was a moderate negative correlation between fundoscopic grading and CRA PSV & EDV in DR with  $p$  value of  $< 0.00001$ . There was a statistically significant reduction in CRA PSV values in cases when compared to controls ( $t = 9.9024$ ;  $p < 0.00001$ ). There was a moderate positive correlation between fundoscopic grading and CRA RI value in DR with  $p$  value of  $< 0.00001$ . There was a significant increase in the CRA RI values in diabetic patients when compared with normal control subjects ( $t = 15.795$ ;  $p < 0.00001$ ).

There was a weak negative correlation between fundoscopic

grading and PCA PSV in DR with  $p$  value of 0.000529 and moderate negative correlation between fundoscopic grading and PCA EDV in DR with  $p$  value of  $< 0.00001$ . There was a statistically significant reduction in PSV values in cases when compared to controls ( $t = 9.92172$ ;  $p < 0.00001$ ). Though there was a strong positive correlation between fundoscopic grading and PCA RI value in DR with  $p$  value of  $< 0.00001$  but the increase in the RI values of PCA in diabetic patients when compared with normal control subjects was insignificant ( $t = 0.1144$ ;  $p = 0.9091$ ).

Table 2 summarizes the correlation and statistical significance of various USG and doppler parameters with that of fundoscopic grading of DR in diabetic patients.

Table 3 shows the correlation and statistical significance of various USG and doppler parameters among cases and controls.

**Table 2: Correlation of USG & Doppler variables with fundoscopic grading in DR**

CORRELATED VARIABLES	N	Correlation (r value)	Significance (p value)
FUNDOSCOPY & OND	50	-0.854	<0.00001
FUNDOSCOPY & ONSD	50	-0.559	0.000024
FUNDOSCOPY & OA PSV	50	-0.589	<0.00001
FUNDOSCOPY & OA EDV	50	-0.684	<0.00001
FUNDOSCOPY & OA RI	50	0.750	<0.00001
FUNDOSCOPY & CRA PSV	50	-0.692	<0.00001
FUNDOSCOPY & CRA EDV	50	-0.684	<0.00001
FUNDOSCOPY & CRA RI	50	0.724	<0.00001
FUNDOSCOPY & PCA PSV	50	-0.473	0.000529
FUNDOSCOPY & PCA EDV	50	-0.738	<0.00001
FUNDOSCOPY & PCA RI	50	0.766	<0.00001

**Table 3: Comparison & Correlation USG & Doppler variables between Diabetic patients (Cases) and Controls**

COMPARED variables	N	Correlation (t value)	Significance (p value)
OND in cases vs. controls	50	6.187	<0.0001
ONSD in cases vs. controls	50	1.835	0.6948
OA PSV in cases vs. controls	50	7.893	<0.00001
OA EDV in cases vs. controls	50	11.029	<0.00001
OA RI in cases vs. controls	50	15.654	<0.00001
CRA PSV in cases vs. controls	50	9.902	<0.00001
CRA EDV in cases vs. controls	50	13.653	<0.00001
CRA RI in cases vs. controls	50	15.795	<0.00001
PCA PSV in cases vs. controls	50	9.921	<0.00001
PCA EDV in cases vs. controls	50	3.831	<0.000225
PCA RI in cases vs. controls	50	0.114	0.909133

Table 4 shows the comparison and correlation of USG and doppler parameters among controls and diabetic patients with no DR.

## Discussion

DR is the most common microvascular complication of type 2 diabetes [4]. Failure of good glycemic control leads to worsening of ocular neurovascular damage and can even render a patient blind. Early detection of ocular changes can halt progression of DR to sight threatening PDR and warn a patient about poor, inadequate glycemic control.

The current routine practices for detection and grading of DR include – fundoscopic examination, fluorescein angiography and optical coherence tomography. However early pathological changes in the retinal vasculature can be quantitatively identified by doppler imaging while changes are inconspicuous/imperceivable on routine ophthalmoscopic examinations. In addition, CDI also has a high sensitivity in detecting commonly associated complications such as vitreous hemorrhage and retinal detachment.

Males outnumbered females in our patient study group - suggesting higher prevalence of diabetes in males. This is similar to that published in IDF 2019 atlas which stated that there were approximately 17.2 million more men than women living with diabetes [12].

In our study, we noted an inverse correlation between the fundoscopic grading and measured velocity (PSV, EDV) of arteries (i.e., lesser velocities noted with increasing grades of DR). The increase in resistive index (RI) was directly proportional to the fundoscopic grading. Also, there was a

significant decrease in arterial (OA, CRA and PCA) PSV and EDV in cases when compared to controls. The increase in resistive index of OA and CRA in cases was significant when compared to that of controls. There was an increase in the RI of PCA of diabetics when compared to that of controls, however it was statistically insignificant.

We also found that there was a significant decrease in velocities of OA and CRA among diabetic patients with no retinopathy when compared to control subjects. This suggests that color Doppler imaging can be used as an early diagnostic tool for detecting changes in ocular vessels prior to their visibility on fundoscopy.

There was also a significant correlation between OND and fundoscopic grading. Decrease in diameters was noted in higher grades of DR. However, the change in OND among control subjects and diabetic patients with no retinopathy was statistically insignificant. This suggests that involvement of the nerve in diabetes occurs later in the course of the disease (unlike arterial involvement which occurs early). Several studies suggest that the value of RI is more reliable as it is not angle/direction dependent [13-15].

Khandelwal et al in their study found EDVs of OA and CRA in patients with diabetes to be significantly lower than those of normal subjects [16]. They also reported the blood flow velocities in the minimal DR group to be decreased in all three blood vessels, i.e., OA, CRA, and PCA. The study revealed that despite the absence of retinopathy, the RI of OA was significantly greater in diabetic patients as compared to normal individuals [16]. Sood et al. in their on NPDR patients reported an increase in RI of CRA and PCA as compared to baseline ocular blood flow parameters [17].

**Table 4: Comparison & correlation of variables between Controls and Diabetic patients with no DR**

COMPARED variables	N	Correlation (t value)	Significance (p value)
OND	50	-0.183	0.855
ONSD	50	-1.846	0.069
OA PSV	50	2.794	0.006775
OA EDV	50	7.571	<0.00001
OA RI	50	-15.767	<0.00001
CRA PSV	50	4.041	0.00014
CRA EDV	50	7.948	<0.00001
CRA RI	50	-13.1	<0.00001
PCA PSV	50	4.813	<0.00001
PCA EDV	50	-1.303	0.196849
PCA RI	50	1.027	0.308079

Mohammad Ghasem Hanafi et al. also suggested that mean RI in patients with PDR was significantly higher (0.83) than the healthy control group (0.54) [18].

Karami et al. also observed that the RI and PI of retrobulbar arteries in individuals with diabetic retinopathy were significantly higher than normal subjects [19]. MacKinnon et al. also suggested that ophthalmic artery RI in proliferative retinopathy (0.81) was higher than healthy individuals (0.72) [20]. These findings were comparable to our present study and show that hemodynamic alterations in retrobulbar circulation appear before clinical ocular manifestations of DR [21].

Mohammad Ghasem Hanafi et. al. reported ophthalmic artery RI in minimal DR group to be significantly lower than PDR [18].

### Limitations of study

- Our study excluded patients with comorbidities such as hypertension and coronary artery disease which would affect the ocular circulation. However, in reality and daily practice diabetic patients usually present with many other noncommunicable diseases such as obesity, hypertension, metabolic disorder etc.
- We were unable to assess correlation between duration of diabetes and vascular changes as majority of patients are unable to recall the duration and are diagnosed after many years of latent undetected disease.

### Summary and Conclusion

Type 2 diabetes is commonly associated with ocular neurovascular alterations that develop over a period of time and usually escape attention until late in the disease. These changes can be optimally detected with a high degree of accuracy by ultrasound and color doppler imaging. Thus, doppler imaging can be used as a screening tool for early detection of diabetic retinopathy.

**Conflict of Interest:** All authors declare no COI

**Ethics:** There is no ethical violation as it is based on voluntary anonymous interviews

**Funding:** No external funding

**Guarantor:** Dr. (Prof.) Nitishkumar Yeslawath will act as guarantor of this article on behalf of all co-authors.

### References

- 1) International Diabetes Federation, 2019 ATLAS, 9TH EDITION, ISBN: 978-2-930229-87-4 atlas@idf.org. Pg.14
- 2) International Diabetes Federation, 2019 ATLAS, 9TH EDITION, ISBN: 978-2-930229-87-4 atlas@idf.org. pg.44
- 3) Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-53

- 4) Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med*. 2012;366(13):1227-1239.
- 5) Sabanayagam C, Banu R, Chee ML, Lee R, Wang YX, Tan G, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol*. 2019;7(2):140-9.
- 6) Schmetterer L, Wolzt M. Ocular blood flow and associated functional deviations in diabetic retinopathy. *Diabetologia* 1999;42(4):387-405.
- 7) Chihara E, Matsuoka T, Ogura Y, Matsumura M. Retinal nerve fiber layer defect as an early manifestation of diabetic retinopathy. *Ophthalmology* 1993;100(8):1147-51.
- 8) Meyer-Rusenberg B, Pavlidis M, Stupp T, Thanos S. Pathological changes in human retinal ganglion cells associated with diabetic and hypertensive retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2006;245(7):1009-18.
- 9) Bedi DG, Gombos DS, Ng CS, Singh S. Sonography of the eye. *AJR*. 2006; 87:1061-72.
- 10) Goebel W, Lieb WE, Ho A, Sergott RC, Farhoumand R, Grehn F. Color Doppler imaging: A new technique to assess orbital blood flow in patients with diabetic retinopathy. *Invest Ophthalmol VisSci* 1995;36:86470.
- 11) Hayreh SS. The sheath of the optic nerve. *Ophthalmologica* 1984;189(1-2):54-63.
- 12) International Diabetes Federation, 2019 ATLAS, 9TH EDITION, ISBN: 978-2-930229-87-4 atlas@idf.org. Pg.37
- 13) Gracner T. Ocular blood flow velocity determined by color Doppler imaging in diabetic retinopathy. *Ophthalmologica*. 2004;218:237-242.
- 14) Dimitrova G, Kato S. Color Doppler imaging of retinal diseases: major review. *Surv Ophthalmol*. 2010; 55:193-214.
- 15) Tranquart F, Bergels O, Koskas P, Arsene S, Rossazza C, Pisella PJ, et al. Color Doppler imaging of orbital vessels: personal experience and literature review. *J Clin Ultrasound*. 2003;31:258-73.
- 16) Khandelwal RR, Mundhada PA, Khandelwal RR, Majumdar M, Khandelwal RR, Raje D, et al. Ocular hemodynamic alterations in patients of Type 2 diabetes mellitus: Journal of Clinical Ophthalmology Res. 2017;5:17-22.
- 17) Sood S, Narang S, Kocchhar S, Sarda S, Aggarwal S, Arya SK. Correlation of progression of diabetic retinopathy with the alterations in retrobulbar circulation. *Nepal J Ophthalmol*. 2013;5:14753.
- 18) Hanafi MG, Farahi F, Masoudrad M. Evaluation the index of ophthalmic arteries in diabetic patients with retinopathy compared to diabetic patients without retinopathy using color Doppler ultrasound: International Journal of Medical Research & Health Sciences. 2016;5(12):287-91.
- 19) Karami M, Janghorbani M, Dehghani A, Khaksar K, Kaviani A. Orbital Doppler evaluation of blood flow velocities in patients with diabetic retinopathy. *Rev Diabet Stud*. 2012;9(2-3):104-11.
- 20) MacKinnon JR, McKillop G, O'Brien C, Swa K, Butt Z, Nelson P. Colour Doppler imaging of the ocular circulation in diabetic retinopathy. *Acta Ophthalmol Scand*. 2000;78(4):386-9.
- 21) Dimitrova G, Kato S. Color Doppler imaging of retinal diseases. *Surv Ophthalmol* 2010;55:193214.

