Original Article

# Evaluation of retrobulbar circulation in type 2 diabetic patients using color Doppler imaging

*K Divya, Vikrant Kanagaraju[1], B Devanand[1], C Jeevamala, A Raghuram, D Sundar*

**Purpose:** To investigate the retrobulbar circulatory parameters in type 2 diabetes mellitus patients with color Doppler imaging (CDI) and compare the results with nondiabetic controls. **Methods:** This prospective study included 50 type 2 diabetic patients and 50 age-matched controls. Seven field stereo fundus photography was used to diagnose and classify diabetic retinopathy (DR). Diabetic patients were further divided into two: Group 1, consisted of patients with no DR, mild and moderate non-proliferative DR ($n$ = 36); Group 2, severe nonproliferative and proliferative DR ($n$ = 14). CDI was performed using Philips iU22 xMATRIX ultrasound. The peak systolic velocity (PSV), end-diastolic velocity (EDV), resistivity index (RI) and pulsatile index (PI) of ophthalmic (OA), posterior ciliary artery (PCA), and central retinal artery (CRA) along with central retinal vein (CRV) were recorded. **Results:** RI in the ophthalmic artery was significantly higher in both DR groups than the control group ($P$ = 0.000). Diabetic Group 1 had decreased blood flow velocity (PSV and EDV) in PCA compared to controls ($P$ = 0.046 and $P$ = 0.010, respectively). Group 2 DR had significantly reduced EDV and increased RI in CRA compared to Group 1 ($P$ = 0.015). Binary logistic regression analysis revealed glycosylated hemoglobin and RI of OA to be independent risk factors of DR. **Conclusion:** Significant changes in resistivity index and flow velocities were observed in the retrobulbar vessels, especially in ophthalmic artery in diabetics compared to controls. CDI with results of increased resistance or decreased flow could be useful to predict individuals at higher risk for developing severe DR.

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Ocular manifestations of diabetes are numerous and among them, diabetic retinopathy (DR) is a major clinical issue for ophthalmologists. DR is the most frequent cause of preventable blindness in working-age adults (20–74 years) and is therefore considered as a major public health issue.[1] Though treatable in appropriate stages, the prevention of retinal complications of diabetes and consequent visual impairment is vital to reduce the burden of DR. There is a felt need for better diagnostic modalities and surrogate markers in the evaluation and management of DR.

In spite of decades of research, the mechanisms behind the onset and progression of DR still remain unclear. From a hemodynamic point of view, evidence has shown that there is an early reduction in blood flow to retina before the onset of DR followed by a gradual increase as the retinopathy progresses.[2] Color Doppler imaging (CDI) is an established, safe, and noninvasive ultrasonic method useful for qualitatively and quantitatively assessing the blood flow velocities and indirect blood flow.[3] CDI has been suggested to be valuable in the diagnosis and management of several ocular diseases with altered hemodynamics such as glaucoma, retinal vascular diseases, ischemic optic neuropathy, and ocular ischemic syndrome.[4] An analysis of retrobulbar hemodynamics in diabetes using CDI can provide insight into the pathogenesis and prospective treatment for DR as well as predict those at higher risk of developing vision threatening DR. Several authors have evaluated the circulatory changes in diabetics using CDI and reported conflicting results. While few studies have reported a reduction in the retrobulbar blood flow velocities,[5-7] others have noted an increase[8] or no change.[9] Studies on the resistive index (RI) of orbital vessels which is a measure of peripheral vascular resistance have also shown significant discrepancies.[10,11] Factors such as demographic variables, duration of diabetes, methods of DR assessment, positions of CDI, and sample sizes account for the observed discrepancies. Moreover, most studies have not excluded patients with hypertension and those on medications affecting systemic blood flow which can influence the results. Studies on orbital hemodynamic alterations among type 2 diabetics from India are relatively few. The diabetic population in India is close to hitting the alarming mark of 69.9 million by 2025 and 80 million by 2030, denoting an expected increase of 266%. Hence, India is deemed as the world's capital of diabetes.[12] With increasing prevalence of diabetes and DR, it is important to know the hemodynamic alterations among diabetics from the Indian population.

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The objective of this study was to evaluate the flow velocities and vascular resistance of orbital blood vessels using CDI in a pure cohort of type 2 diabetic patients from India and compare the results with healthy controls.

## Methods

This prospective hospital-based study was carried out at a tertiary care institution from south India between March 2017 and April 2019. The study included consecutive patients of type 2 DM (as per definition of the American Diabetes Association) attending the ophthalmology outpatient clinic for the screening of retinopathy. Exclusion criteria were history of any ocular disease that might affect ocular blood flow such as glaucoma, nondiabetic retinal vascular occlusion, ocular inflammation, high myopia, previous ocular surgery, or panretinal photocoagulation. Patients with systemic hypertension, dyslipidemia, nephropathy, and cardiovascular diseases were excluded from the study. Pregnant and breastfeeding women were not included. Patients taking medications known to affect systemic hemodynamics such as Angiotensin-converting enzyme inhibitors, calcium channel blockers, and anti-migraine drugs were also excluded.

50 age-matched healthy subjects were enrolled as a control group. The control subjects were recruited from individuals attending the department of ophthalmology for a routine eye examination. They were not on any medication and did not have ocular or systemic disease. The study was conducted according to the principles of the Declaration of Helsinki and the study protocol was approved by the institutional ethics committee. Informed consent was obtained from all participants.

Information regarding age, gender, body mass index, duration of diabetes, antidiabetic medications, and blood pressure were obtained from all participants. Serum glycosylated hemoglobin (HbA1c) was determined from fasting venous blood sample.

All study participants underwent a comprehensive ophthalmic examination including dilated fundus with slit-lamp biomicroscope using a 90 diopter lens and indirect ophthalmoscopy. A 30° stereoscopic fundus photograph of 7 standard early treatment diabetic retinopathy study (ETDRS) fields was taken from both eyes of diabetic patients using a digital fundus camera (TRC-50 DX Mydriatic retinal camera; Topcon Medical Systems, Oakland, NJ).

The presence, as well as the severity of diabetic retinopathy, was determined by grading of color fundus photographs following the international clinical disease severity scale for diabetic retinopathy which is based on the findings of WESDR (Wisconsin Epidemiological Study of Diabetic Retinopathy) and ETDRS.[13] The diabetic patients were assigned to one of the following groups namely no retinopathy, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). The

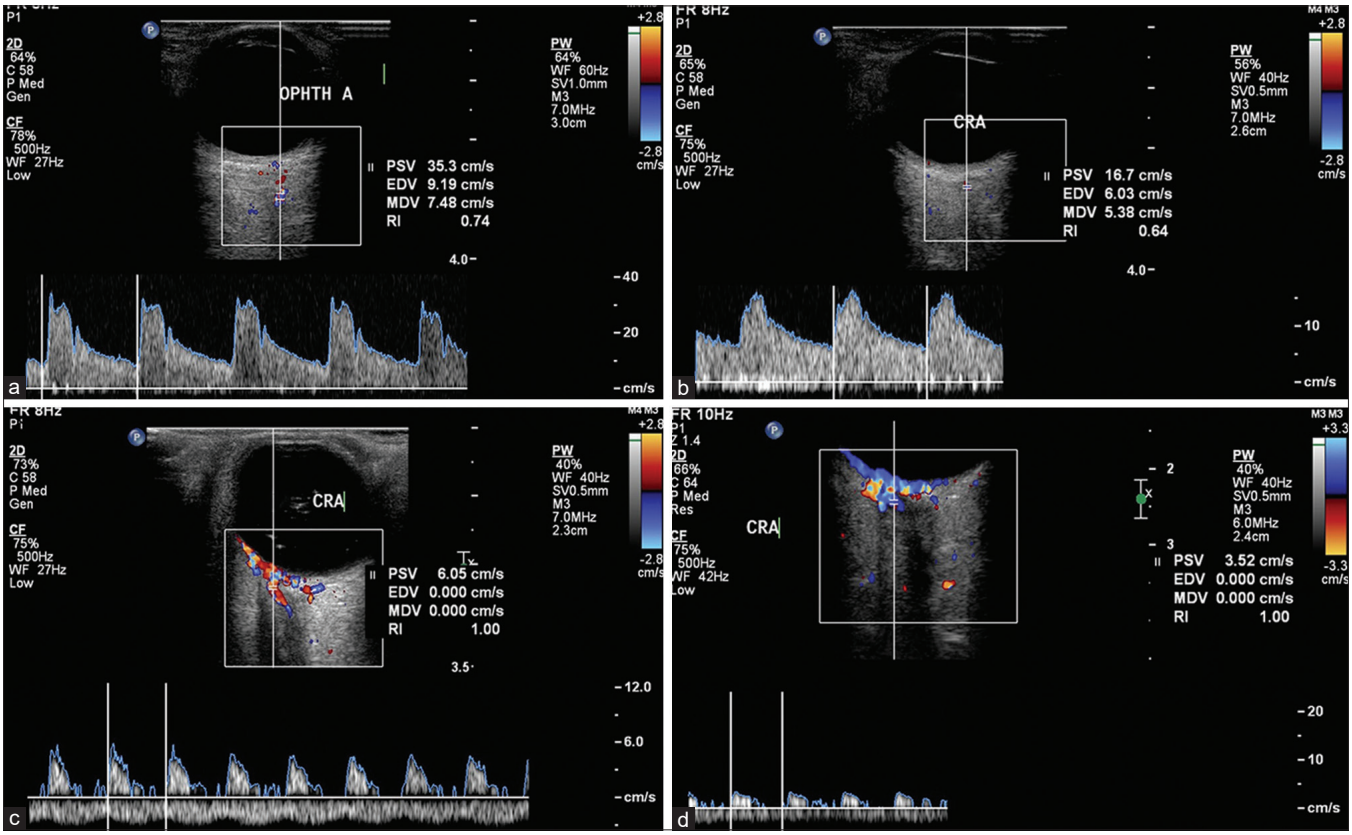


**Figure 1:** (a) Color Doppler image (CDI) showing normal color flow and spectral waveform in ophthalmic artery with preserved M wave pattern; (b) CDI showing normal color flow and spectral waveform in central retinal artery; (c) CDI showing low-velocity monophasic flow in central retinal artery in a patient with moderate NPDR; (d) CDI showing monophasic spectral waveform with absent diastolic flow in central retinal artery in a patient with severe NPDR

eye with worse retinopathy was included in the study. If both eyes had equal retinopathy, the right eye was assigned to the study.

Color Doppler sonography of the eye was performed for cases and controls by a masked expert Radiologist using a color Doppler unit and a 12 to 5 MHZ linear-array transducer (Philips iU22 xMATRIX ultrasound system). The patients were examined in the supine position and care was taken to avoid any undue pressure on the eye. Examiner's hand was rested on the orbital margin and sterile coupling gel was applied over closed eyelids. The Doppler signal was registered online after the cursor was positioned on the region of interest. To reduce errors in measurement of velocities, angle correction was applied to the pulsed Doppler recordings.

The peak systolic velocity (PSV) and end-diastolic velocity (EDV) readings were obtained from the ophthalmic artery (OA), central retinal artery (CRA), and the posterior ciliary artery (PCA). Since the velocity wave in a central retinal vein (CRV) is not in direct relation to the cardiac cycle its hemodynamic parameters were expressed as maximum (V max) and minimum (V min) blood velocity. Signals from the ophthalmic artery were obtained from the medial aspect of the eyeball, superior to the optic nerve. The central retinal artery and vein were located within the optic nerve, around 10 mm behind the eyeball. [Fig. 1] Signals from the temporal branch of the short posterior ciliary artery were located lateral to the optic nerve.

With the help of PSV and EDV, we calculated the vascular resistance expressed by the resistivity index and pulsatile index using Pourcelot's formula.

Resistive index (RI) = (PSV-EDV)/PSV; Pulsatile index (PI) = (PSV-EDV)/Vmean

### Statistical analysis

For statistical analysis diabetic patients were further divided into two groups; Group 1 included patients with no retinopathy, mild NPDR, and moderate NPDR while Group 2 consisted of patients with severe NPDR and PDR.

Statistical analysis was performed using statistical package for social sciences (SPSS, SPSS Inc, Chicago, IL, USA) version 24. Data were expressed as mean ± standard deviation. The normality of data distribution was tested by the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) with a *post hoc* Bonferroni was used for the analysis of normally distributed continuous data. Kruskal-Wallis analysis was used for analyzing non-normally distributed data. A comparison between hemodynamic parameters was calculated by ANOVA followed by Tukey-Kramer *post hoc* comparison. Pearson's coefficient was used to study the correlation between variables.

**Table 1: Demographic and clinical characteristics of controls and diabetic subjects**

| Characteristic | Controls (*n*=50) | Group 1 (*n*=36) | Group 2 (*n*=14) | *P* |
|---|---|---|---|---|
| Age (years) | 56.5±9.00 | 55.5±8.60 | 51.9±5.64 | 0.209 |
| Body mass index (kg/m$^2$) | 23.34±3.62 | 24.81±3.15 | 24.53±3.88 | 0.141 |
| Median Systolic BP (mmHg) | 110 (20) | 120 (18.75) | 125 (12.5) | 0.076 |
| Median Diastolic BP (mmHg) | 70 (30) | 76.5 (10) | 70 (10) | 0.259 |
| Median duration of diabetes (years) | - | 3 (8) | 10 (11) | 0.115 |
| Glycosylated hemoglobin (%) | 5.81±0.29 | 9.09±2.13 | 10.86±2.33 | 0.014* |

BP=Blood pressure; *$P$<0.05

**Table 2: Hemodynamic parameters of retrobulbar blood vessels among controls and patient groups**

| Hemodynamic parameters (cm/s) | Control (*n*=50) | Group 1 (*n*=36) | Group 2 (*n*=14) | *P* |
|---|---|---|---|---|
| OA PSV | 29.72±8.10 | 30.48±9.78 | 28.76±12.84 | 0.838 |
| OA EDV | 6.87±2.69 | 6.34±3.41 | 5.09±3.50 | 0.166 |
| OA RI | 0.75±0.06 | 0.79±0.06 | 0.83±0.05 | 0.000* |
| OA PI | 1.58±0.27 | 1.74±0.30 | 1.86±0.25 | 0.002* |
| CRA PSV | 12.42±3.85 | 10.40±4.87 | 8.42±2.92 | 0.004* |
| CRA EDV | 2.73±1.17 | 2.33±1.27 | 1.27±0.94 | 0.000* |
| CRA RI | 0.77±0.06 | 0.74±0.16 | 0.85±0.11 | 0.019* |
| CRA PI | 1.63±0.30 | 1.65±0.50 | 2.08±0.65 | 0.004* |
| PCA PSV | 15.44±5.61 | 12.81±3.83 | 14.95±5.15 | 0.054 |
| PCA EDV | 4.19±2.23 | 2.97±1.29 | 3.33±1.63 | 0.011* |
| PCA RI | 0.73±0.06 | 0.75±0.08 | 0.78±0.08 | 0.061 |
| PCA PI | 1.45±0.24 | 1.58±0.37 | 1.68±0.45 | 0.044* |
| CRV V max | 6.14±1.63 | 6.12±1.66 | 5.85±2.07 | 0.853 |
| CRV V min | 3.51±0.97 | 3.34±0.89 | 3.02±1.05 | 0.243 |
| CRV RI | 0.41±0.11 | 0.44±0.11 | 0.46±0.08 | 0.329 |
| CRV PI | 0.60±0.24 | 0.65±0.25 | 0.70±0.17 | 0.350 |

OA=Ophthalmic artery; CRA=Central retinal artery; PCA=Posterior ciliary artery; CRV=Central retinal vein; PSV=Peak systolic velocity; EDV=End diastolic velocity; V max=Maximum blood velocity; V min=Minimum blood velocity; RI=Resistivity index; PI=Pulsatility index; *$P$<0.05

Binary logistic regression analysis was performed to determine independent risk factors for retinopathy. All tests for statistical significance were two-tailed and performed assuming a type I error probability of <0.05.

## Results

### Demographic and clinical parameters

The study included 52 males and 48 females. The age of patients ranged from 41 to 76 years. The duration of diabetes ranged from 6 months to 20 years. Among the diabetic patients, 29 were on oral hypoglycemic agents, 9 were on insulin, and 12 were on combination therapy. Group 1 ($n$ = 36) consisted of 16 patients with no DR, 13 with mild NPDR, and 7 with moderate NPDR. Group 2 ($n$ = 14) consisted of 6 patients with severe NPDR and 8 with PDR. There were no statistically significant differences in the age, body mass index and blood pressure between controls and diabetic groups. Glycosylated hemoglobin (HbA1c) levels were found to be significantly higher in Group 2 diabetic patients ($P$ = 0.014). No significant difference was noted in the duration of diabetes among diabetic groups. The demographic and clinical characteristics of controls and diabetic subjects are presented in Table 1.

### Hemodynamic parameters

Table 2 shows the hemodynamic parameters of retrobulbar blood vessels among controls and patient groups.

*Ophthalmic artery*

Significant differences were noted in the RI and PI values of the ophthalmic artery between controls and diabetic patients with various DR grades. OA flow velocities did not vary between groups.

**Table 3: Pearson correlation coefficients between the duration of diabetes, HbA1c, and hemodynamic parameters**

| Variable | Duration of diabetes | HbA1c |
|---|---|---|
| OA PSV | 0.021 (0.885) | -0.120 (0.407) |
| OA EDV | -0.141 (0.328) | -0.055 (0.706) |
| OA RI | 0.314* (0.026) | 0.097 (0.504) |
| OA PI | 0.299* (0.035) | 0.078 (0.588) |
| CRA PSV | -0.135 (0.349) | -0.269 (0.059) |
| CRA EDV | -0.464* (0.001) | -0.299*(0.035) |
| CRA RI | 0.375* (0.007) | -0.046 (0.753) |
| CRA PI | 0.487* (0.000) | 0.131 (0.370) |
| PCA PSV | -0.052 (0.722) | 0.170 (0.239) |
| PCA EDV | -0.234 (0.102) | 0.196 (0.172) |
| PCA RI | 0.332* (0.019) | -0.075 (0.606) |
| PCA PI | 0.321*(0.023) | -0.085 (0.556) |
| CRV V max | 0.134 (0.354) | 0.128 (0.375) |
| CRV V min | -0.143 (0.322) | -0.058 (0.687) |
| CRV RI | 0.390* (0.005) | 0.172 (0.233) |
| CRV PI | 0.415*(0.003) | 0.210 (0.144) |

Corresponding P values are shown in brackets. HbA1c=Glycosylated hemoglobin; OA=Ophthalmic artery; CRA=Central retinal artery; PCA=Posterior ciliary artery; CRV=Central retinal vein; PSV=Peak systolic velocity; EDV=End diastolic velocity; V max=maximum blood velocity; V min=minimum blood velocity; RI=Resistivity index; PI=Pulsatility index; *$P$<0.05

*Central retinal artery and vein*

The hemodynamic parameters of CRA were significantly different between controls, DR Group 1, and Group 2 whereas no such difference was seen in the CRV. *Post hoc* comparison revealed a significantly reduced PSV and EDV of CRA ($P$ = 0.005 and 0.000, respectively) along with increased PI ($P$ = 0.003) in DR group 2 compared to controls. Patients with group 2 DR also demonstrated a significant decrease of EDV and increased RI of CRA compared to group 1 ($P$ = 0.015). PSV, EDV, and RI of CRA did not differ significantly between controls and DR group 1.

*Posterior ciliary artery*

The EDV and PI of PCA were found to vary significantly between controls and diabetic groups. Significant reduction in PSV and EDV of PCA was noted in DR group 1 compared to controls ($P$ = 0.046 and $P$ = 0.010, respectively after *post hoc* comparison).

### Relation between duration of diabetes, HbA1c, and hemodynamic parameters

Duration of diabetes correlated positively with the resistive and pulsatile indices of all retrobulbar vessels studied namely ophthalmic artery, CRA, PCA, and CRV. HbA1c levels, as well as the duration of diabetes, were found to correlate negatively with EDV of CRA. No correlation was found between duration of diabetes and HbA1c levels ($R$ = 0.183, $P$ = 0.203). Table 3 shows the relationship between duration of diabetes, HbA1c levels, and hemodynamic parameters.

Binary logistic regression analysis revealed that HbA1c levels and RI of OA were independent risk factors of retinopathy.

## Discussion

The main observations of our study are as follows: (1) RI in the ophthalmic artery was significantly higher in both DR groups than the control group and was an independent risk factor of retinopathy, (2) Patients with Group 1 DR had decreased blood flow velocity (PSV and EDV) in the posterior ciliary artery compared to control group, (3) Patients with Group 2 DR had significantly reduced EDV and increased RI in the CRA compared to Group 1, (4) Compared to the control group, patients with Group 2 DR had slower flow velocities and increased PI in CRA but RI values did not vary significantly.

Our finding of decreased EDV in the posterior ciliary artery in patients with Group 1 DR supports the hypothesis that choroidal blood flow is affected in the early stages of DR. Laser Doppler flowmetry has shown decreased choroidal blood flow in the foveal region in early DR.[14] Choroidal vascularity index (CVI) analysis by swept-source optical coherence tomography (OCT) has also shown reduced CVI in patients with mild/moderate NPDR.[15] Cao *et al.* have reported a 4 times more choriocapillary loss in diabetic eyes compared to non-diabetic eyes in histopathologic studies.[16] Ferrara *et al.* have demonstrated the loss of intermediate and large blood vessels in the Sattler's layer and Haller's layers in diabetic eyes in choroidal OCT.[17] Our observation of decreased EDV in the PCA suggests increased peripheral vascular resistance of the choroidal circulation in early DR and is in concordance with these studies. Dimitrova *et al.* reported decreased EDV and increased RI in PCA in patients

with background DR compared to controls in CDI of diabetic patients performed in sitting posture.[6] The authors have suggested that erect posture during CDI measurement is essential to appreciate significant alterations in posterior ciliary circulation. Supine posture has been suggested to increase EDV and decrease the RI.[18] As autoregulation and autonomic nervous responses are altered in diabetics, the correlation of change in circulatory parameters between normal individuals and diabetics associated with postural variation may not be expected to be equal. However, CDI was performed in supine posture in our patients. Our observations could be attributed to the shorter duration of diabetes in our patients than theirs.

RI in OA was higher in both DR groups compared with controls in our study. These findings are similar to those of previous studies.[5,19] Basturk *et al.* evaluated the association between the resistivity index of orbital arteries and DR in 91 types 2 diabetics with microalbuminuria using CDI. The authors have demonstrated increased RI values of all orbital arteries in patients with DR compared to those without DR and controls. RI value of ≥ 0.72 in OA indicated the presence of DR with 78.4% sensitivity and 70% specificity.[10] Our finding of increased RI in the OA in both DR groups can be attributed to the statistically nonsignificant reduction in EDV observed in diabetic subjects because of downstream vascular changes in the retina and choroid. We did not observe significant differences in CRA parameters between controls and DR Group 1. Hence, we believe that the OA hemodynamic parameters in our study probably represent alterations in choroidal blood flow. It has been suggested that of the total ocular blood supply from OA, less than 10% flows to the retina while the remainder is directed to choroid via the ciliary circulation due to the high metabolic demand of photoreceptors.[20] Moreover, the diastolic blood flow of PCA is higher than CRA since these vascular channels of choroid have low resistance.[21]

**Table 4: Various published studies on ocular circulation in diabetic patients using color Doppler imaging**

| Study | Country | Sample size | Duration of diabetes (years) | Findings |
|---|---|---|---|---|
| Arai *et al.*, 1998[9] | Japan | 74<br>Controls: 22<br>NDR: 27<br>DR: 25 | NA | Significant increase in RI of CRA in patients with DR compared to those without DR and controls ($P$<0.01) |
| MacKinnon *et al.*, 2000[5] | Scotland | 62<br>Controls: 17<br>NDR/BDR: 24<br>PPDR/PDR: 21 | NDR/BDR: 10<br>PPDR/PDR: 12 | Significant decrease in both PSV and EDV of CRA in the PPDR/PDR group compared to NDR/BDR and control group ($P$<0.05) while RI showed no significant change.<br>RI of OA was increased in diabetics compared to controls. |
| Dimitrova *et al.* , 2001[6] | Japan | 95<br>Controls: 22<br>NDR: 38<br>BDR: 35 | NDR: 9.0±7.2<br>BDR: 18. 9±11.2 | Significant decrease in EDV and increase in RI of PCA in BDR group compared to controls ($P$=0.01 and 0.0003, respectively) |
| Gracner *et al.*, 2004[8] | Slovenia | 66<br>Controls: 22<br>NPDR: 22<br>SNPDR/PDR: 22 | 13.5±9.31 | Significant increase in PSV of OA in the SNPDR/PDR group compared to controls.<br>Significant increase in RI of PCA in SNPDR/PDR group compared to NPDR and controls |
| Sullu *et al.*, 2005[7] | Turkey | 34<br>Controls: 20<br>PDR: 14 | 13.5±6.1 | Decrease in mean EDV and increase in RI of both OA and CRA in PDR compared to controls ($P$<0.05) |
| Baydar *et al.*, 2007[11] | Australia | 44 (65 eyes)<br>Controls: 11<br>Diabetics: 33 | 4.94±3.90 | The RI of CRA was significantly higher in the control group than in the NDR group.<br>RI of OA was significantly higher in NDR than in the moderate NPDR group. |
| Basturk *et al.*, 2012[10] | Turkey | 118<br>Controls: 27<br>NDR: 40<br>DR: 51 | NDR: 6.87±4.37<br>DR: 8.23±2.55 | Patients with DR had significantly higher mean RIs of OA, CRA and PCA compared to those without DR and controls ($P$<0.001) |
| Karami *et al.*, 2012[30] | Iran | 123<br>Controls: 25<br>BDR: 74<br>PPDR: 24 | BDR: 5.6±0.7<br>PPDR: 12.6±1.1 | RI of OA and CRV were significantly higher in patients with DR compared to controls ($P$<0.005) |
| Our study | India | 100<br>Controls: 50<br>NDR/mild/ moderate NPDR: 36<br>SNPDR/PDR: 14 | NDR/mild/moderate NPDR: 8<br>SNPDR/PDR: 11 | RI of OA was significantly increased in diabetics compared to controls.<br>Significant decrease in both PSV and EDV of PCA in mild/ moderate NPDR compared to controls ($P$<0.05)<br>Significantly reduced EDV and increased RI of CRA in SNPDR/PDR compared to mild/moderate NPDR group ($P$=0.015) |

NDR=No diabetic retinopathy; BDR=Background diabetic retinopathy; PPDR=Preproliferative diabetic retinopathy; NPDR=Nonproliferative diabetic retinopathy; SNPDR=Severe nonproliferative diabetic retinopathy; PDR=Proliferative diabetic retinopathy; OA=Ophthalmic artery; CRA=Central retinal artery; PCA=Posterior ciliary artery; CRV=Central retinal vein; PSV=Peak systolic velocity; EDV=End diastolic velocity; RI=Resistivity index; NA=Not available

Khatri *et al.* assessed the correlation between RI of OA and topographic alterations of retinal pigment epithelium (RPE) on spectral-domain optical coherence tomography (SD-OCT).[22] In their study involving 75 patients with type 2 diabetes and 24 controls, a significant increase in OA RI was noted with the severity of DR ($F = 14.23$, $P < 0.001$). A positive correlation was noted between RI of OA and grades of RPE alterations on SD-OCT suggesting that decreased blood flow contributes to RPE dysfunction. Studies demonstrating early retinal damage in experimental diabetes have reported morphological changes in RPE and animal studies have also shown reduced choroidal blood flow in young diabetic animals suggesting that blood flow deficit could be an early pathological change in DR.[23,24] Although it is difficult to propose a causal association it can be postulated that changes in choroidal circulation (as reflected by increased RI of OA) lead to downregulation of antiangiogenic PEDF (pigment epithelial-derived factor) and upregulation of VEGF (vascular endothelial growth factor) thereby contributing to progression of DR. Differential expression and secretion of these growth factors derived from the retinal pigment epithelium have been suggested to lead to nonproliferative and proliferative DR.[25]

Patients with Group 2 DR had significantly reduced EDV in the CRA compared to Group 1 DR as well as healthy controls. Our observations are in line with previous studies.[5,6,8] These can be attributed to the increased peripheral vascular resistivity with the progression of DR. Pathological findings in DR such as capillary basement membrane thickening, retinal capillary leukostasis, loss of retinal capillaries, and altered blood rheology support this circulatory feature.[2,26,27]

Another observation of our study was that DR Group 2 had significantly reduced flow velocity in the CRA but an increase in RI was not statistically significant compared to the control group. This can be due to the concomitant decrease of both PSV and EDV in patients with Group 2 DR. Neudorfer *et al.* evaluated the long-term changes in the retrobulbar circulation of 138 eyes of diabetic subjects at a 10-year follow-up.[28] Patients were divided into four groups, namely, nondiabetic controls, diabetics without DR, nonproliferative DR, and proliferative DR. RI values of CRA and PCA had increased in the two no retinopathy groups and in the nonproliferative DR group, with a surprising nonsignificant decrease in the proliferative DR group. The authors have concluded that an increase of resistance in the retrobulbar blood vessels due to DR can decrease over time and may even be reversed. It has been suggested that the decrease in resistance reflects the beginning of an increase in retinal blood flow with the progression of DR due to the short-circuiting of the obstructed retinal capillary network.[28] This is supported by histopathologic studies, which have shown areas of capillary closure being traversed by preferential dilated anastomotic channels.[29]

Our finding of a positive correlation between duration of diabetes and RI of all retrobulbar vessels was similar to the observations of Karami *et al.*[30] We found negative correlation between EDV of CRA and duration of diabetes as well as HbA1c levels ($R = -0.464$, $P = 0.001$; $R = -0.299$, $P = 0.035$, respectively). Poor glycemic control (as reflected by increased HbA1c) and longer duration of diabetes can be associated with increased peripheral vascular resistance and thus reduced EDV in CRA. Our findings of HbA1c and RI of OA as independent risk factors of DR are similar to that of Basturk *et al.*[10]

Table 4 shows the various published studies on ocular circulation in diabetic patients using CDI.

Our study has several strengths. None of the diabetic patients had associated vascular diseases. Hypertension as well as antihypertensive medications significantly alter the resistive indices of blood vessels and therefore confound the results. We intentionally excluded these patients to study the influence of diabetes alone on ocular hemodynamics. A single masked, experienced radiologist performed all the Doppler examinations gently with the least pressure on the globe thus eliminating interobserver variability. The presence and severity of DR were graded based on seven field stereo fundus photography for accuracy.

To our knowledge, this study is the first of its kind in a pure cohort of diabetics from India.

There are a few limitations to our study. The sample size was small which accounts for the limited subgroup analysis. CDI provides information on blood flow velocity only and absolute volumetric blood flow cannot be quantified since it is not possible to study the diameter of retrobulbar vessels with CDI accurately. In spite of this limitation, blood velocity is probably a good indicator of blood flow within a given vessel.[31,32] Moreover, measurement of retinal blood flow is difficult and no accurate method to quantitatively assess perfusion is currently used clinically.

## Conclusion

In conclusion, significant changes in the blood flow velocities and RI were observed in the retrobulbar vessels, especially in an ophthalmic artery in diabetics compared to controls. RI could be potentially useful for early diagnosis and follow-up of DR. CDI with results of increased resistance or decreased flow can be of help to identify diabetic individuals at higher risk for developing severe DR. This is especially useful in patients with opaque media where conventional methods are of little use.

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### Conflicts of interest

There are no conflicts of interest.

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