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Original Research Article

Comparison of retrobulbar circulation in type 2 diabetics and non-diabetics using color Doppler imaging

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ABSTRACT

Purpose: To record the resistivity index (RI), peak systolic velocity (PSV) and end-diastolic velocity (EDV) in the retrobulbar circulation and predict the progression of diabetic retinopathy (DR).

Materials and Methods: Forty patients with type 2 diabetes (DM) and forty non-diabetics patients attending the outpatient clinic for an eye examination were enrolled after informed consent. All study participants underwent a comprehensive ophthalmic examination including dilated fundoscopy. The diabetic patients were assigned to groups based on ETDRS grading of diabetic retinopathy. Color Doppler of the eye was performed on all the enrolled individuals. The peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index readings were recorded from the ophthalmic artery(OA), central retinal artery (CRA), and the posterior ciliary artery (PCA).

Result: The values acquired from OA showed a significant increase in RI and a significant decrease in PSV and EDV with the advancement of DR. The parameters PSV and EDV recorded from CRA, as were also decreased DR progressed. This decrease was clinically significant RI index recorded from CRA first displayed a rise with the appearance of DR and a notable decline from severe NPDR to PDR. As DR progressed, PCA parameters revealed a decrease in PSV and EDV and RI.

Conclusion: Significant changes in the resistivity index and flow velocities were observed in the retrobulbar vessels of the two groups. In this study, the results of decreased flow velocity with the progression of diabetes support the rheological changes involved in the pathophysiology of diabetes. The resistance index shows an significant increase with the progression of DR. These could be useful to predict individuals at higher risk for developing severe DR or PDR.

1. Introduction

Diabetic retinopathy (DR) is one of the many visual symptoms of diabetes that poses a significant problem for public health. In adults aged 20 to 74, it is the most prevalent cause of avoidable blindness.[1] Treatment at the right time, prevents advanced diabetic ocular manifestations that is severe visual impairment and thus lessens the burden of diabetic retinopathy. Diabetic Retinopathy (DR) is known to cause blindness and affects 4.2 million people globally.[1,2] It is the primary cause of irreversible blindness. As the frequency of diabetes mellitus is on the rise, ocular complications of diabetes also show an increasing trend simultaneously.

Strict metabolic and blood-pressure control has been shown to significantly decrease the risk of development as well as progression of retinopathy and remains the cornerstone in the medical management of DR. Laser photocoagulation and vitrectomy are the treatments available for complications of DR. Treatment can prevent

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blindness, but the key success of therapy lies in recognizing the patients with retinopathy before the vision is affected and predicting the progression of the retinopathy. In this study, we look for such characteristics that aid in DR progression prediction. Improved surrogate indicators and diagnostic methods are necessary for the assessment and treatment of DR. Even after decades of study, it is still unknown what pathogenic alterations cause DR to begin and worsen. According to a few hemodynamic studies, blood flow to the retina is first reduced before the onset of DR and then gradually increased as the retinopathy worsens.[3] Colour Doppler imaging (CDI) is a safe, non-invasive ultrasonic technique that can measure blood flow parameters quantitatively and qualitatively.[4] The detection and treatment of several ocular illnesses can be aided by colour Doppler imaging of the retrobulbar circulation. These primarily include several ocular diseases with altered blood flow like retinal vascular diseases, ocular ischemic syndrome, glaucoma, and ischemic optic neuropathy.[5] The same can be applied to the examination of retrobulbar circulation hemodynamics in diabetes to predict those who are more likely to develop vision-threatening DR and to shed light on the etiology and potential therapy of DR.[6]

2. Materials and Methods

This prospective study was carried out in a tertiary care hospital in South India between June 2021 to December 2021. The study included forty individuals with type 2 DM and forty non-diabetics attending the outpatient clinic for an eye examination. Individuals with a history of any ocular disease with altered ocular blood flow like glaucoma, nondiabetic retinal vascular occlusion, ocular inflammation, high myopia, previous ocular surgery, or pan-retinal photocoagulation or systemic conditions like hypertension, dyslipidemia, nephropathy, and cardiovascular diseases were excluded from the study. Pregnant and breastfeeding women and patients taking medications like Angiotensin-converting enzyme inhibitors, and calcium channel blockers, were all excluded. Informed consent was obtained from individuals enrolled following which they underwent a comprehensive ophthalmic examination including dilated fundoscopy. The diabetic patients were assigned to groups based on ETDRS grading of diabetic retinopathy that is no retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR).

Using Philips-iU22-xMATRIX-ultrasound, the same board-certified radiologist conducted CDIs (color Doppler imaging) on every enrolled patient. The hand of the examiner rested on the orbital edge while the patients were evaluated in a supine position. After applying sterile coupling gel to the closed eyelids, CDI was carried out. Ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary artery (PCA) were imaged and the values were obtained namely, resistivity index, peak systolic velocity (PSV), and end-diastolic velocity (EDV).

Above the optic nerve, on the medial aspect of the globe, the recordings from the ophthalmic artery were obtained. Ten millimeters behind the globe, in the substance of the optic nerve, were the central retinal artery and vein recordings. Laterally, signals from the temporal branch of the small posterior ciliary artery were received.

3. Results

The study included 45 males and 35 females. The patients were aged between 39 to 76 years. The duration of diabetes ranged from 6 months to 35 years. Among the diabetic patients, 29 patients were on oral hypoglycemic agents hypoglycemic agents insulin respectively. The diabetics were divided into groups based on the fundus changes. Group 0 consisted of 10 patients with no DR, Group 1 of 10 patients with mild to moderate NPDR, Group 2 of 8 patients with severe NPDR, and Group 3 of 10 patients with PDR.

The flow parameters of the ophthalmic artery are shown in Table 1. The ophthalmic artery in diabetics revealed a considerable increase in RI which was clinically not significant. A decrease in PSV and EDV were also noted which was significant ($p< 0.001$) in comparison to non-diabetics.

Table 1: Flow parameters recorded with ophthalmic artery

OA	Diabetics	Non diabetics	P value
PSV	26.3 (24.5 - 33.1)	53.3 (45.1 - 58.7)	<0.001
RI	0.78 (0.74 - 0.81)	0.76 (0.74 - 0.78)	0.241
EDV	5.2 (4.7 - 5.4)	12.7 (11.7 – 14.5)	<0.001

OA: Ophthalmic artery; PSV: Peak systolic velocity; RI: Resistivity index; EDV: End diastolic velocity

The flow parameters of the central retinal artery are noted in Table 2. In diabetics, a significantly reduced flow velocity, PSV and EDV, and elevated RI were noted in comparison to the parameters recorded in non-diabetics.

Table 2: Flow parameters recorded from central retinal artery

CRA	Diabetics	Non diabetics	P Value
PSV	17.8 (16.6 – 19.0)	22.5 (17.2 – 25.8)	<0.001
RI	0.79 (0.76 – 0.82)	0.72 (0.67 – 0.76)	<0.001
EDV	1.3 (0.9 – 3.8)	5.7 (5.2 – 5.9)	<0.001

CRA: Central retinal artery; PSV: Peak systolic velocity; RI: Resistivity index; EDV: End diastolic velocity

3.1.

3.1.1. Posterior ciliary artery

Table 3 shows the parameters obtained from the posterior ciliary artery. The indices in diabetics showed a non-significant and significant decrease in PSV and EDV respectively, whereas RI showed an increase.

Table 3: Flow parameters recorded from the posterior ciliary artery

PCA	Diabetics	Non diabetics	P Value
PSV	13.0 (12.3 – 14.9)	13.0 (11.5 – 15.6)	0.984
RI	0.76 (0.72 – 1.1)	0.66 (0.64 – 0.70)	<0.001
EDV	2.7 (0.9 – 3.5)	4.8 (4.0 – 5.3)	<0.001

PCA: Posterior ciliary artery; PSV: Peak systolic velocity; RI: Resistivity index; EDV: End diastolic velocity

3.2. Progression of diabetic retinopathy and hemodynamic parameters in diabetics

3.2.1. Ophthalmic artery

With the commencement of DR, PSV and EDV recorded showed a non-significant decrease with onset, advancement of retinopathy, and appearance of PDR. RI showed a non-significant increase in appearance and advancement of retinopathy whereas a significant reduction (p 0.000) with appearance of PDR was noted. Table 5 shows a comparison of the blood flow parameters with grades of retinopathy. The highlighted values have been considered.

3.2.2. Central retinal artery

With the commencement of DR, PSV recorded showed a non-significant decrease with onset, advancement of retinopathy, and appearance of PDR. EDV recorded showed a significant decrease with onset of retinopathy in early disease and appearance of PDR subsequently. RI showed a significant increase in the appearance and advancement of retinopathy whereas a significant reduction (p 0.000) with the appearance of PDR was noted. Table 5 shows a comparison of the blood flow parameters with grades of retinopathy. The highlighted values have been considered.

3.2.3. Posterior ciliary artery

With the commencement of DR, PSV recorded showed a non-significant decrease with onset, advancement of retinopathy, and appearance of PDR. EDV recorded showed a significant decrease with the onset of retinopathy in early disease and a non-significant decrease with higher grades of retinopathy and the appearance of PDR subsequently. RI showed a significant decrease in the appearance of retinopathy and a non-significant decrease with the advancement of retinopathy. Table 5 shows a comparison of the blood flow parameters with grades of retinopathy. The highlighted values have been considered.

4. Discussion

In our study, we observed a reduction of PSV and EDV with an increase in RI in the retrobulbar vessels in diabetics compared to non-diabetics. This can be attributed to the downstream vascular changes in the retina and choroid in diabetes where the pathogenesis involves diabetic vasculopathy.

Vasculopathy entails molecular alterations such as endothelial dysfunction and damage,[7] a pro-inflammatory state driven by elevated circulation of cytokines, chemokines, and reactive oxygen species that harm the media and intima of the arterial wall.[8] Vasoregulation is lost as a result of these impairments, and vasoconstriction is observed.[9] Furthermore, patients with diabetes exhibit higher proliferation of vascular smooth muscle cells and a more synthetic phenotype that is associated with vascular dysfunction. These changes can result in tunica media layer thickening and narrowing of the arterial lumen.[10] Pro-thrombotic and atherosclerotic alterations are also observed.All these changes reflect the stasis of blood with increasing vascular resistance to flow which supports the observation of our study. This observation is similar to the study by Gracner et al, where he found a significant elevated PSV of OA in the NPDR/PDR group as compared to controls.[11]

Basturk et al. examined the relationship between DR and the orbital artery resistance index in 91 type 2 diabetic patients who also had microalbuminuria using CDI. The authors have shown that, in comparison to controls and patients without DR, patients with DR had higher RI values for all orbital arteries.[12]

Amongst the diabetics, the observation seen which is PSV reduction with the progression of DR can also be explained by the pathophysiology involved in diabetic vasculopathy.

EDV of PCA significantly decreases in diabetics and as DR progresses. This provides credence to the theory that early in the course of DR, choroidal blood flow is impacted which is supported by studies that show reduced choroidal blood flow on laser Doppler flowmetry at the fovea in the early stages of DR.[13] In Choroidal OCT of diabetic eyes were studied by Ferrara et al. and have shown loss of big and intermediate blood vessels in the Satler's and Haller's layers.[14] These observations are consistent with our finding of lower EDV in the PCA, which points to increased peripheral vascular resistance of the choroidal circulation in early DR.

Khatri et al. evaluated the relationship between the topographic changes of the retinal pigment epithelium (RPE) on spectral-domain optical coherence tomography (SD-OCT) and flow parameter RI of OA. Reduced blood flow is one of the contributing factors to RPE dysfunction, as evidenced by the positive correlation seen between the RI of OA and the grades of RPE alterations on SD-OCT.[15]

Table 4: Mean values of the hemodynamic parameters recorded

	OA PSV (cm/s)	OA RI	OA EDV (cm/s)	CRA PSV (cm/s)	CRA RI	CRA EDV (cm/s)	PCA PSV (cm/s)	PCV RI	PCA EDV (cm/s)
Group 0	34.56	0.82	3.92	16.83	0.80	3.94	12.89	1.23	3.56
Group 1	27.86	0.78	5.16	16.00	0.92	1.30	15.09	0.76	3.18
Group 2	25.11	0.77	5.26	18.69	0.78	0.88	12.34	0.76	0.92
Group 3	21.10	0.73	5.54	17.85	0.72	1.10	12.84	0.72	0.79

PSV: Peak systolic velocity; RI: Resistivity index; EDV: End diastolic velocity; OA: Ophthalmic artery; CRA: Central retinal artery; PCA: Posterior ciliary artery
Group 0: No DR, Group 1: Mild to moderate NPDR, Group 2: Severe NPDR, Group 3: PDR

Table 5: P values obtained from comparison of the mean values of the hemodynamic

	OA PSV	OA RI	OA EDV	CRA PSV	CRA RI	CRA EDV	PCA PSV	PCV RI	PCA EDV
p-value for group 0,1	**.14**	**.02**	**.02**	**.17**	**.00**	**.00**	**.22**	**.00**	**.04**
p-value for group 0,2	.00	.00	.00	.41	.01	.00	.46	.00	.00
p-value group 0,3	.00	.00	.00	.19	.00	.00	.22	.00	.00
p-value for group 1,2	**.07**	**.02**	**.15**	**.10**	**.00**	**.52**	**.17**	**.41**	**.00**
p-value for group 1,3	.00	.00	.00	.25	.00	.00	.48	.00	.00
p-value for group 2,3	**.06**	**.00**	**.04**	**.46**	**.00**	**.00**	**.83**	**.03**	**.00**

PSV: Peak systolic velocity; RI: Resistivity index; EDV: End diastolic velocity; OA: Ophthalmic artery; CRA: Central retinalartery; PCA: Posterior ciliary artery
Group 0: No DR, Group 1: Mild to moderate NPDR, Group 2: Severe NPDR, Group 3: PDR
Parameters recorded from each of the 4 groups (Mann Whitney U test)
Highlighted parameters have been considered as follows:
1. Comparison of group 0 and group 1- Onset of DR
2. Comparison of group 1 and group 2- Progression of DR
3. Comparison of group 2 with group 3- Progression to PDR

Changes in choroidal circulation, which are evidenced by greater RI of OA and hence lower flow, accelerate the progression into DR. Due to these modifications, VEGF (vascular endothelial growth factor) is overexpressed and antiangiogenic PEDF (pigment epithelial-derived factor) is downregulated. Differential expression and release of these growth factors, which are produced from the retinal pigment epithelium, have been suggested to be the cause of NPDR progression.[16]

In contrast to this study, our study didn't show a significant increase in RI of the Ophthalmic artery with the progression of DR but showed a significant decrease with progression to PDR.

With the onset of DR, the RI of CRA showed a rise. However, as severe NPDR progressed to PDR, the RI of CRA significantly decreased. Over time, a DR-related increase in resistance in the retrobulbar blood arteries may diminish or even reverse. This can be explained by the proposed theory that the drop in resistance, signals the onset of an increase in retinal blood flow because of the development of new, fragile, low-resistance shunt capillaries and the short-circuiting of the clogged retinal capillary network, which is classical of PDR.[17]

5. Conclusion

The decrease in PSV of retrobulbar circulation in this study indicates a DR progression. The development of diabetic retinopathy and its progression can be monitored by the parameter RI of PCA, CRA, and OA. With the advancement of DR, the RI increases. More precisely, the rise in RI of CRA indicates the onset of DR, which, during follow-up, shows a decrease with the onset of PDR. As a result, it can serve as a guide to transition from severe NPDR to PDR, which has enormous therapeutic implications. A decrease in velocity of EDV of the vessels PCA and CRA denotes the advancement of diabetic retinopathy and can be closely monitored as an index. In individuals with no DR, EDV of ophthalmic artery can be monitored to assess the onset of DR. The onset and course of diabetic retinopathy can be predicted using colour Doppler imaging of the retrobulbar circulation.

6. Source of Funding

None.

7. Conflict of Interest

None.

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