Original article

Correlation of progression of diabetic retinopathy with the alterations in retrobulbar circulation

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Abstract

Introduction: Color Doppler Imaging (CDI) is used widely to study retrobulbar circulation. **Objectives:** To determine the association between progression of diabetic retinopathy (DR) and alterations in retrobulbar arterial circulation using CDI studies. **Materials and methods:** Prospective observational case series. It is single institutional study of 50eyes of nonproliferative diabetic retinopathy in 50 patients with type II diabetes mellitus. DR was graded according to ETDRS system. Retrobulbar circulation was studied in patients for Peak systolic velocity (PSV), End diastolic velocity (EDV) and Resistive index (RI) in Central retinal artery (CRA), Ophthalmic artery (OA) and Posterior ciliary artery (PCA) using CDI initially and reevaluated after 6 months or later for any change in retinopathy grade and arterial circulation parameters. The patients were grouped as Group I not showing progression of DR and Group II showing progression. The two groups were compared for any significant change in CDI parameters. **Results:** The baseline resistive indices were higher than normal population. There was significant increase in RI in PCA and CRA in all patients after 6 months. 14 patients (28%) showed progression of DR and 36 (72%) did not show progression of DR. There was no significant association with progression of retinopathy and CDI findings. (p=>0.05). **Conclusion:** The retrobulbar arterial circulation seems to be affected in all diabetics with DR. The changes appear to be progressive. The CDI findings in arterial circulation however lack predictive power for progression of diabetic retinopathy in non proliferative DR.

Keywords: Retrobulbar arterial circulation, diabetic retinopathy, Color Doppler imaging

Introduction

Ever since the introduction of Doppler ultrasound in evaluation of retrobulbar circulation (Erickson et al , 1989), it has been used widely to study various ophthalmologic disorders. Color Doppler imaging is a noninvasive method to detect the flow of blood in retrobulbar blood vessels with good reliability and reproducibility (Williamson et al, 1994; Matthiessen, 2004). It has been used to study diabetic retinopathy (Göbel et al, 1995; Güven,1996).Many clinical aspects of diabetes mellitus have been studied using CDI such as proliferative diabetic retinopathy, effect of pan retinal photocoagulation in proliferative diabetic retinopathy (Mendivil et al, 1995a, 1995b,1996,1997,1998), choroidal circulation in diabetics (Dimitrova et al, 2001), progression to proliferative diabetic retinopathy (Dimitrova et al, 2003; Tomaz Gracner, 2004), type 1 diabetic children and adolescent without diabetic retinopathy (Gulgun et al, 2008), type 1

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diabetic retinopathy and dyslipidemia (Modrzejewska et al, 2008).The present study was carried out to study the correlation of changes in retrobulbar circulation with progression of no-proliferative diabetic retinopathy in patients with type II diabetes mellitus.

Material and methods

This was a prospective study of 50 eyes of 50 patients with type II diabetes mellitus of more than 5 years duration. The study was approved by the institutional review board. Initially, data from both the eyes of each patient was recorded. At the final follow up of e" 6 months only one eye of each patient was included. In the case of a patient showing progression of DR, the eye with progression was included in the study. Any increase in grade of diabetic retinopathy from previous evaluation was considered as progression. In cases where progression was bilateral and in the non-progression group, data from the right eye was included in the analysis, unless that eye had been subjected to laser photocoagulation or any surgery in the past.

We excluded eyes with metabolically unstable diabetes, diagnosed cases of glaucoma , myopia > 6 diopters, history of intra ocular surgery or ocular trauma within preceding three months, eyes without diabetic retinopathy or having proliferative diabetic retinopathy, and with significant media opacities precluding fundus photography. Proliferative diabetic retinopathy cases were not included as further progression in these cases was difficult to comment. A detailed history was taken. All patients were subjected to baseline systemic investigations which included - fasting blood sugar (FBS), post prandial blood sugar (PPBS), glycosylated blood sugars (HbA1c), lipid profile, 24 hour urinary proteins, blood urea and serum creatinine, blood pressure and ECG to confirm metabolic control. The patients were subjected to detailed stereoscopic ocular examination with slitlamp and +90D and +20D lens. Intraocular pressure was recorded with Goldmannapplanation tonometer. Fundus photography in 7 fields of Airlie House classification (DRS report No 7, 1981) was done for all patients using Zeiss Retinal Digital Imaging system. Baseline fundus fluorescein angiography was carried out for all patients. On the basis of their fundus photographs, the diabetic retinopathy was graded into mild, moderate, severe and very severe NPDR according to ETDRS system (ETDRS report no 12, 1991) using standard photographs 2A and 8A at the time of enrollment.

All patients were subjected to Color Doppler Imaging using 5 - 7.5 MHz transducer on Hewlett Packard (Image Point) Imaging System. It was performed with the patient lying supine, eyes closed and gaze directed upwards and the Color Doppler probe applied with contact jelly through the closed upper lid. Three consecutive readings were taken to avoid any effect of the respiratory cycle upon the velocities. Arteries that were imaged include the central retinal artery, posterior ciliary artery and ophthalmic artery. The parameters that were studied were peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI). PSV and EDV are obtained from the fastest velocities in systole and diastole respectively. Resistive index (PSV-EDV/PSV) is usually quoted from 0 to 100% (or 0 to 1) with 0 representing no resistance and 100 representing highest resistance.

All patients were seen at 3 months, 6 months and 3 monthly thereafter with a minimum of 6 months follow up. At each visit, a detailed clinical examination, fundus photography, fundus fluorescein angiography and color Doppler imaging were done. The grading of DR, and color Doppler parameters of last visit were considered to look for progression of diabetic retinopathy. For the purpose of statistical analysis, eyes were retrospectively grouped into Group I (eyes not showing progression of DR) and Group II (eyes showing progression of DR).

Results

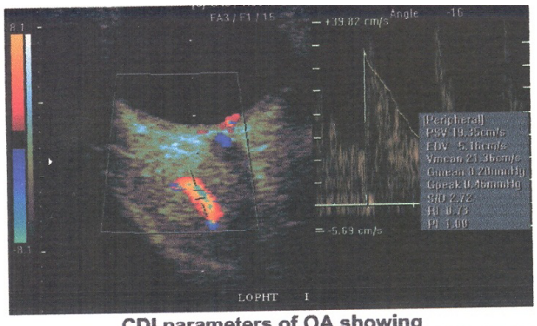
The study included 28 (56 %) males and 22 (44%) females. The age of patients ranged from

38 to 75 years (mean age 55.8 ± 8.4 years). The duration of diabetes ranged from 6 years to 25 years (mean 12.9 ± 5.5 years). Twelve patients (44%) were on insulin treatment and 38 (76%) were on oral hypoglycemic agents (OHA's) only for control of their diabetes. None of the patients were on diet control. Systemic parameters were well controlled throughout the study period for all. At the initial visit, 27 patients (54%) were graded to have mild non-proliferative diabetic retinopathy (NPDR) and 23 (46%) to have moderate NPDR and none of patients had severe NPDR. Of these patients, 14 (28%) had clinically significant macular edema (CSME) for whom modified grid laser treatment was done. The follow up period ranged from 6 months to 2 years (mean follow up period being 12.20 ± 3.2 months). The mean values of retrobulbar circulatory parameters at the initial visit and last follow-up visit are given in Table 1.

Table 1: Mean color doppler index parameters of patients at initial and final visit

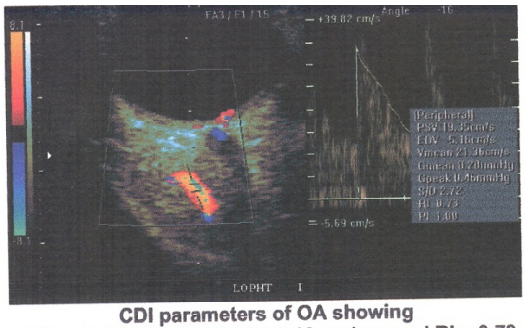
	Peak systolic velocity (cm/s)		End diastolic velocity (cm/s)		Resistive index	
	Initial	***Final***	***Initial***	***Final***	***Initial***	***Final***
Ophthalmic artery	33.42 ± 18.02	36.97 ± 13.47	9.12 ± 4.93	8.09 ± 3.69	0.75 ± 0.07	0.76 ± 0.08
Central retinal artery	14.28 ± 11.21	17.72 ± 7.57	5.64 ± 3.81	4.29 ± 2.71	0.67 ± 0.10	0.78 ± 0.10
Posterior ciliary artery	15.36 ± 7.17	20.71 ± 11.68	3.44 ± 1.88	4.62 ± 2.85	0.65 ± 0.14	0.76 ± 0.12

Figures 1a to 1c show the CDI parameters at the initial visit (Figure 1).



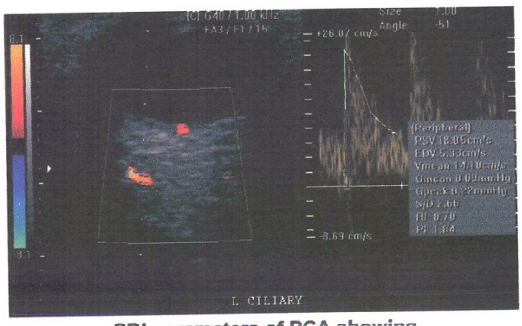
CDI parameters of OA showing
PSV = 19.35 cm/sec, EDV = 5.16 cm/sec and RI = 0.73

Figure 1 a



CDI parameters of OA showing
PSV = 19.35 cm/sec, EDV = 5.16 cm/sec and RI = 0.73

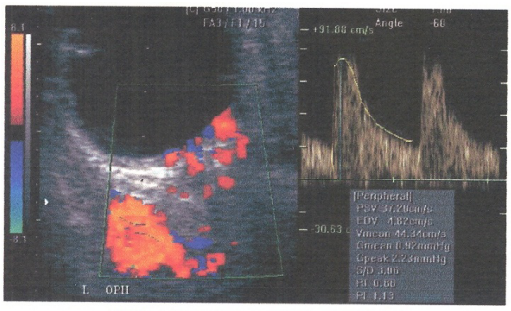
Figure 1 b



CDI parameters of PCA showing
PSV = 18.05 cm/sec, EDV = 5.33 cm/sec and RI = 0.70

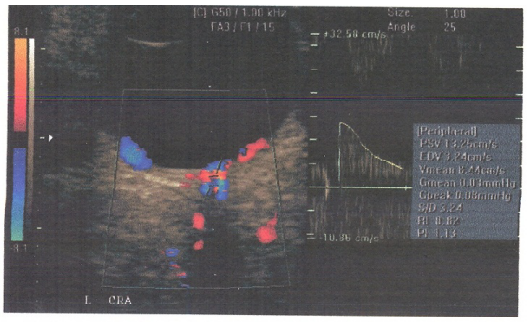
Figure 1 c

The final visit CDI parameters are reflected in figures 2a to 2c (Figure2).



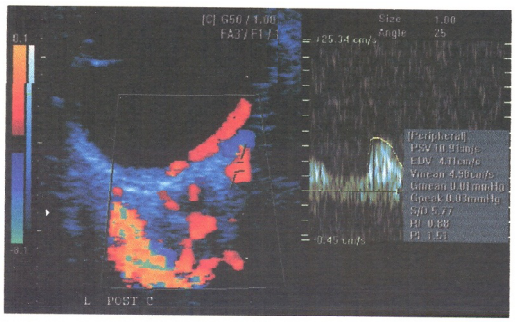
CDI parameters of OA showing
PSV = 37.20 cm/sec, EDV = 4.82 cm/sec and RI = 0.86

Figure 2 a



CDI parameters of CRA showing
PSV = 13.25 cm/sec, EDV = 3.24 cm/sec and RI = 0.82

Figure 2 b



CDI parameters of PCA showing
PSV = 10.91 cm/sec, EDV = 4.11 cm/sec and RI = 0.88

Figure 2 c

When the patients were assessed at the final visit, 36 patients (72%) showed no progression in the status of their diabetic retinopathy (Group I) and 14 patients (28%) showed progression (Group II). Of the initial 27 patients having mild NPDR, only 19 (70.37%) remained as mild NPDR, 4 (14.8%) progressed to moderate NPDR, 2(7.4%) to severe NPDR, 2 (7.4%) to PDR at last follow up. Of the initial 23 patients having moderate NPDR, 17 (73.91%) continued to have moderate NPDR, 2 (8.69%) progressed to severe NPDR, 4 (17.39%) to PDR. The groups were comparable for age, duration, type of treatment, associated systemic diseases like hypertension and nephropathy. All patients were metabolically stable diabetics and progression of disease could not be attributed to hypertension, heart or kidney problems. The mean duration of diabetes was comparable in the two groups, 12.56 ± 5.10 years and 13.86 ± 6.62 years in groups I and II respectively.

Both the groups had statistically comparable values at the final follow-up in the inter-group analysis ($p > 0.05$) (Table 2).

Table 2: Inter group comparison of retrobulbar circulatory parameters at baseline and last follow up visit

			Group 1 (no progression in diabetic retinopathy)	Group 2 (progression in diabetic retinopathy)	P value (p<0.05)
Baseline retrobulbar circulatory parameters	OA1	PSV	33.95 ± 16.75cm/s	32.31 ± 21.60cm/s	0.78
		EDV	10.08 ± 5.74cm/s	7.18 ± 1.76cm/s	0.21
		RI	0.74 ± 0.08	0.77 ± 0.07	0.21
	CRA1	PSV	14.65 ± 12.39cm/s	13.32 ± 7.67cm/s	0.71
		EDV	5.84 ± 4.16cm/s	5.21 ± 3.18cm/s	0.73
		RI	0.67 ± 0.10	0.70 ± 0.10	0.36
	PCA1	PSV	14.78 ± 6.66cm/s	16.84 ± 8.45cm/s	0.37
		EDV	3.11 ±1.71cm/s	4.16 ± 2.16cm/s	0.23
		RI	0.65 ± 0.12	0.64 ± 0.18	0.80
At last follow up visit	OA2	PSV	36.15 ± 13.53cm/s	39.10 ± 13.57cm/s	0.49
		EDV	8.38 ± 4.00cm/s	7.24 ± 2.54 cm/s	0.36
		RI	0.76 ± 0.07	0.77 ± 0.09	0.50
	CRA2	PSV	18.16 ± 7.84cm/s	16.60 ± 6.98cm/s	0.51
		EDV	4.40 ± 2.57cm/s	3.98 ± 3.20cm/s	0.65
		RI	0.76 ± 0.10	0.82 ± 0.13	0.11
	PCA2	PSV	22.53 ± 11.99cm/s	16.03 ± 9.72cm/s	0.08
		EDV	5.08 ± 3.06 cm/s	3.22 ± 1.49cm/s	0.07
		RI	0.75 ± 0.09	0.08 ± 0.16	0.14

OA - Ophthalmic artery , CRA - Central retinal artery, PCA - Posterior cilliary artery, PSV -Peak systolic velocity, EDV- End diastolic velocity, RI- Resistive index

Table 3: Intra group comparison of retrobulbar circulatory parameters during first and last visit

			1st measurement	Last measurement	P-value (p<0.05)
Group 1 (no progression in diabetic retinopathy)	OA_1-OA_2	PSV	33.95 ± 16.76 cm/s	36.15 ± 13.53 cm/s	0.55
		EDV	10.08 ± 5.74 cm/s	10.00 ± 3.52 cm/s	0.96
		RI	0.74 ± 0.08	0.76 ± 0.07	0.23
	CRA_1-CRA_2	PSV	14.65 ± 12.39 cm/s	18.16 ± 7.84 cm/s	0.18
		EDV	5.84 ± 4.16 cm/s	4.40 ± 2.81 cm/s	0.20
		RI	0.67 ± 0.10	0.76 ± 0.10	0.00006
	PCA_1-PCA_2	PSV	14.78 ± 6.66 cm/s	22.53 ± 11.99 cm/s	0.00109
		EDV	3.11 ± 1.71 cm/s	4.21 ± 3.13 cm/s	0.29
		RI	0.65 ± 0.12	0.75 ± 0.09	0.00018
Group 2 (progression in diabetic retinopathy)	OA_1-OA_2	PSV	32.31 ± 21.61 cm/s	39.10 ± 13.57 cm/s	0.18
		EDV	7.65 ± 1.91 cm/s	7.09 ± 2.23 cm/s	0.69
		RI	0.77 ± 0.08	0.77 ± 0.93	0.97
	CRA_1-CRA_2	PSV	13.32 ± 7.67 cm/s	16.60 ± 6.98 cm/s	0.25
		EDV	5.52 ± 3.84 cm/s	5.62 ± 2.71 cm/s	0.96
		RI	0.70 ± 0.10	0.82 ± 0.13	0.008
	PCA_1-PCA_2	PSV	16.84 ± 8.45 cm/s	16.03 ± 9.72 cm/s	0.84
		EDV	5.01 ± 1.87 cm/s	3.20 ± 0.97 cm/s	0.08
		RI	0.64 ± 0.18	0.80 ± 0.16	0.02

OA - Ophthalmic artery, CRA - Central retinal artery, PCA - Posterior ciliary artery, PSV - Peak systolic velocity, EDV - End diastolic velocity, RI - Resistive index

However, in the intra-group analysis when the last color Doppler measurement was compared with first readings, both the groups had a significant increase in the resistive index in CRA and PCA with increasing duration of diabetes (Table 3).

Discussion

Diabetic retinopathy is a potentially blinding disease and remains an important public health problem. There is limited literature available regarding changes in retrobulbar circulation. The present study was carried out to ascertain the predictive role of retrobulbar arterial circulation in the progression of NPDR in NIDDM patients. In the present study, RI was higher in NIDDM patients than when compared to available data of the normal population in literature (Williamson et al, 1995, 1996). PSV and EDV in central retinal artery and PSV, EDV and RI in posterior ciliary arteries appeared to be significantly different from those of the normal population. However, circulatory parameters of larger vessels like the ophthalmic artery did not differ significantly from those of the non-diabetic population.

In the present study, RI in CRA and PCA increased significantly in all the NIDDM eyes with diabetic retinopathy as duration of disease increased despite adequate metabolic control. However, no correlation was found between diabetic retinopathy progression and alteration of retrobulbar arterial circulation during this follow-up. The RI is a measure of blood flow and it is inversely proportional to the blood flow. RI in various arteries seemed to increase over a period of time in all diabetic patients. These results demonstrate that all diabetic patients with retinopathy suffer from increased blood flow resistance in the major vessels feeding the eye. However, certain other factors contribute to the development of proliferative disease or progression of diabetic retinopathy.

Konno et al (1996) conducted a study on IDDM patients using Laser Doppler flowmetry and monochromatic photography. They took measurements of temporal retinal artery and found that as the duration of diabetes increases and as the disease become more severe, there is a transition from negative to positive retinal blood flow slopes. They found that blood speeds

in the retinal arteries of patients with IDDM are significantly lower than normal. They further observed that the arterial blood speeds were already low before clinical appearance of retinopathy.

Dimitrova et al (2001) studied choroidal circulation in diabetic patients and found that not only the retina but also the choroidal circulation is affected in diabetics. They found posterior ciliary artery circulatory alterations in NDR (no diabetic retinopathy) and BDR (background diabetic retinopathy) patients suggesting choroidal circulatory dysfunction. The increased posterior ciliary artery resistive index (RI) in NDR patients suggested reduced vessel wall compliance in the choroid that is present in all diabetics irrespective of the presence of DR. A similar pattern of circulatory changes was detected in all the three measured arteries (central retinal, posterior ciliary, and ophthalmic artery) comprising decreased EDV and increased RI in BDR patients, which indicates an increase in ocular peripheral vascular resistivity. In the present study, only NIDDM patients with non-proliferative diabetic retinopathy were included and decreased vessel wall compliance and increased resistivity was seen in CRA and PCA. However, OA did not show any significant difference from normal population. These changes increased over the period of follow-up. Thus, the changes in retrobulbar circulation of PCA and CRA could have bearing on the development of diabetic retinopathy.

Dimitrova et al (2003) studied longitudinally the changes in retrobulbar circulation with progression of diabetic retinopathy. They found that with progression of DR, there was a significant increase in PSV, EDV and RI in the central retinal vein but not in the central retinal artery and posterior cilliary artery. They concluded that the initial changes in the retrobulbar circulation during DR progression occur in the central retinal vein only and the arterial retrobulbar circulation does not seem to guide the progression of DR. In our study also, changes in retrobulbar arterial circulation do not seem to guide the progression, as the changes were present in both progressive and non-progressive groups.

Tomaz Grachner (2004) found a significant increase in the resistive index in the posterior cilliary artery in the PDR group as compared to NPDR and healthy controls. In our study, PDR patients were excluded from the study and a significant increase in the resistive index in both the posterior ciliary artery and the central retinal artery was seen in all diabetic patients whether the retinopathy progressed or not.

Gulgun YO et al (2008) found a significant increase in the resistive index in the posterior cilliary arteries and a significant decrease in RI in ophthalmic artery in young patients with type 1 DM without diabetic retinopathy as compared to healthy controls. RI in these arteries appears to be a function of the duration of diabetes mellitus and short term changes are not associated with progression of diabetic retinopathy. But the relation of this irregularity to disease progression requires extensive research. Thus, the arterial circulation in diabetes is less compliant and has a higher RI.

There have been some lacunae in the present study relating to the small sample size that was evaluated and the short duration of follow-up . The follow up period in the present study might not have been long enough for the clinically apparent progression of DR. It may be probably more useful to conduct a prospective study involving a large number of patients with a longer follow-up and compare values within individual patients over time and then make comparisons between the best and worst quartiles in terms of retinopathy grades.

Conclusion

In the present study, alterations in the retrobulbar arterial circulation do not seem to predict the progression of diabetic retinopathy and development of proliferative disease in NIDDM patients. The retrobulbar arterial circulation appeared to be affected in all diabetics and the changes appear to progress with increasing duration in all diabetics. However, apart from the vascular supply, certain other factors seem to play a role in progression of diabetic retinopathy.

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