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Research Article

Alteration in Hemodynamic Parameters in Ophthalmic and Central Retinal Arteries in Indian Patients with Increasing Grade of Diabetic Retinopathy

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Abstract

Background: Diabetes, with and without retinopathy, is often associated with hemodynamic alterations in ocular blood flow. Color Doppler Imaging (CDI) is an established noninvasive technique that enables measuring blood flow velocities in small orbital vessels.

Aim: We set out tomeasure ocular blood flow hemodynamics by Color Doppler Imaging in the Ophthalmic Artery (OA) and central retinal artery (CRA) in patients with Diabetic Retinopathy (DR) and to compare it with healthy subjects.

Methods: We evaluated 61 eyes of 61 subjects, (controls: 21 and diabetics: 40). Diabetic patients were further classified in two groups: diabetics with either no retinopathy or background retinopathy (NDR/BDR; n=20), and diabetics with preproliferative or proliferative retinopathy (PPDR/PDR; n=20). Three Color Doppler parameters: Peak Systolic Velocity (PSV in cm/s), end diastolic velocity (EDV, cm/s) and Resistivity Index (RI) were measured in the OA and CRA. Statistical analysis was done using ANOVA and Post-Hoc (Tukey) test to compare the results between NDR/BDR, PPDR/PDR and control groups.

Results: No significant difference was seen in the age of the subjects. We found statistically significant differences only in the OA. Specifically, PSV was significantly greater in NDR/BDR Vs controls (95%CI: 2.25 to 14.92); EDV was significantly decreased in PPDR/PDR as compared to controls (95%CI: 0.43 to 4.12) and NDR/BDR (95%CI: 0.13 to 3.80); RI was significantly increased in PPDR/PDR (95%CI: 0.09 to 0.23) and NDR/BDR (95%CI: 0.03 to 0.17) as compared to controls.

Conclusion: We found significant circulatory alterations in the OA in diabetic patients suggesting hemodynamic dysfunction. RI was significantly increased in diabetics as compared to controls.

Keywords: Color Doppler; Diabetic Retinopathy; Hemodynamics; Metabolic Disorders.

Abbreviations: DM- Diabetes Mellitus; DR- Diabetic Retinopathy ; CDI- Color Doppler Imaging; OA- Ophthalmic Artery; NDR- No Diabetic Retinopathy; BDR- Background Diabetic Retinopathy; PPDR- Preproliferative Diabetic Retinopathy; PDR- Proliferative Diabetic Retinopathy; CRA- Central Retinal Artery; PSV- Peak Systolic Velocity; EDV- End Diastolic Velocity; RI- Resistive Index; CI- Confidence Interval.

Introduction

Diabetes Mellitus (DM) is a systemic metabolic disorder, which may result in generalized macrovascular and microvascular complications. The macrovascular complications, accounting for most of the morbidity and mortality, [1-3] include ischaemic heart disease, cerebrovascular disorders and peripheral vascular disease [4]. Microvascular complications include retinopathy, neuropathy and nephropathy. Diabetic Retinopathy (DR), although a microangiopathy, has been shown to independently predict macrovascular events including ischaemic heart disease and stroke [5-7].

DR affects retinal microvasculature leading to characteristic alterations in retinal blood flow [8]. Ocular vascular hemodynamic parameters are often evaluated using Color Doppler Imaging (CDI) and laser Doppler velocimetry [8,9]. CDI is an established noninvasive technique that enables both quantitative and qualitative assessment of blood flow velocities in small orbital vessels as well as simultaneous visualization of 2-D imaging. Using this technique, good reproducibility has been reported in the localization and hemodynamic measurement within the Central Retinal Artery (CRA) and ophthalmic artery (OA) [10]. Many conditions like central retinal

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artery and vein occlusions, vasculitis, and ischemic optic neuropathy are associated with changes in orbital hemodynamics and CDI has successfully demonstrated them [11].

Methods

After clearance from the Institutional Ethics Committee following the tenets of the Declaration of Helsinki and obtaining informed consent, we recruited 61 subjects: 21 controls and 40 cases of diabetes. The control group was randomly selected from those without any ocular pathology, systemic hypertension, diabetes mellitus or vascular disease. Diabetics were diagnosed if they had a fasting plasma glucose ≥ 126 mg/dl or 2-h plasma glucose ≥ 200mg/dl [12]. We included only one eye from both controls and cases (in case of difference in retinopathy, the eye with greater severity was chosen). The cases were further divided into diabetics with no retinopathy or Background Diabetic Retinopathy (NDR/BDR) (corresponds to retinopathy level 2-3) and Preproliferative Diabetic Retinopathy(PPDR) (retinopathy level 4-5)/ Proliferative Diabetic Retinopathy (PDR) (retinopathy level 6-7) as per modified Airlie House system on the basis of dilated retinal examination using the biomicroscopic indirect ophthalmoscope and fundus photographs by a single experienced ophthalmologist [13,14]. The PPDR and PDR were grouped together because of few patients with proliferative (n=4) changes. We excluded diabetic patients who had undergone laser photocoagulation, had any ocular trauma or ocular surgery; we also excluded diabetics who had glaucoma, uveitis, retinal pathology like central retinal vein occlusion, and optic nerve disease. We evaluated only those patients who had systolic blood pressure below 140mmHg and diastolic pressure below 90mmHg. As only single reading of blood pressure was taken and higher blood pressure causes varied volume flow at different times, therefore we excluded this factor.

The CDI of OA and CRA was performed using Color Doppler (Logic 500 pro series, GE) with 5-9 MHz linear array multi frequency probe. After explaining the procedure, scan was performed with the patient supine, eyes closed and gaze directed towards the ceiling. We used a standardized Doppler technique [11]. The transducer was coupled to the closed upper eyelid with sterile ophthalmic methyl cellulose gel. Once optimal visualization of blood flow was obtained on the visual display unit, specific ocular vessels could then be rapidly examined using pulsed Doppler. With slight angular adjustment of the probe, from the spectral analysis of the resulting Doppler frequency shift, a velocity waveform was obtained. The probe angle was always less than 60 degrees, and every measurement was made at constant angle to the vessel. The color Doppler display was set so that blood towards the transducer appeared red, while blood flow away appeared blue. The main outcomes measured were Peak Systolic Velocity (PSV): representing the maximum flow velocity recorded during each cardiac cycle; End Diastolic Velocity (EDV): recorded immediately before the next systolic upstroke; and Resistivity Index (RI) = PSV-EDV/PSV calculated by Pourcelot's formula. RI (also known as Pourcelot's ratio) usually varies from 0% (no resistance) to 100% (high resistance) [11]. Measurements of PSV, EDV, and RI were obtained using the mean of 3 cardiac cycles.

We analyzed the results using ANOVA and Post-Hoc (Tukey) test, significance was set at p≤0.05 (two tailed) and95% CI are also reported.

Table 1: Baseline Characteristics of controls and diabetic groups.

	Controls	NDR/BDR	PPDR/PDR
Number (n)	21	20 (12/8)	20 (16/4)
Mean age (±SD) & range in years	45.81(±3.20) 43-55	49.5 (±9.8) 30-70	50.5 (±7.0) 40-60
Gender (M/F)	8:13	11:9	14:6
Hypertension (Y/N) Mean systolic blood pressure (±SD) in mmHg Mean diastolic blood pressure (±SD) in mmHg	0:21 124(±8) 78(±6)	1:19 128(±10) 82(±7)	7:13 132(±5) 81(±4)
Smoking (Y/N)	2:19	0:20	1: 19
Type of Diabetes Mellitus (Type 2:1 DM)		**19:1**	**19:1**

Results

Table 1 shows baseline characteristics of controls and diabetics. The blood flow parameters of the OA were significantly different among controls, NDR/BDR, and PPDR/PDR ($p<0.05$) (Table 2), while no such difference was seen in the CRA. Specifically, in the OA, a significantly increased PSV was found in NDR/BDR but only when compared to controls (95%CI: 2.25 to 14.92), a significant reduction in EDV of PPDR/PDR group was noticed as compared to both, controls (95%CI: 0.43 to 4.12) and NDR/BDR group(95%CI: 0.13 to 3.80),

Table 2: Mean (±SD) of blood flow parameters in OA and CRA.

	Controls (n=21)	NDR/BDR (n=20) [mean(±SD)]	PPDR/PDR (n=20) [mean(±SD)]	p-value
Ophthalmic artery				
PSV (cm/s)	23.13(±9.02)	31.73(±7.57)	26.82(±8.58)	0.007
EDV (cm/s)	7.63(±2.65)	7.36(±2.45)	5.35(±1.93)	0.009
RI	0.64(±0.09)	0.74(±0.08)	0.81(±0.09)	<0.001
Central retinal artery				
PSV (cm/s)	13.68(±4.52)	13.90(±3.90)	12.51(±3.20)	0.49
EDV (cm/s)	5.81(±2.46)	5.04(±2.24)	4.08(±1.47)	0.07

while significantly higher RI was seen in both NDR/BDR (95%CI: 0.03 to 0.17) and PPDR/PDR (95%CI: 0.09 to 0.23) as compared to controls (Table 3).

Discussion

In our study, PSV was increased in early stages of diabetic retinopathy. Reduced cellular oxygenation in diabetes may demand a compensatory increase in vascular flow. The lack of subsequent further increase in the more advanced retinopathy group could be because sustained and prolonged hyperglycemia may disrupt the normal auto regulatory and homeostatic mechanisms; something quite possible as diabetes persists [15]. We found a decrease in EDV, which points to presence of increase in distal vascular resistance [16]. Increase in RI

Table 3: Intergroup comparison of blood flow parameters in OA.

OA	Controls-NDR/ BDR	Controls-PPDR/ PDR	BDR-PDR
PSV			
Mean difference	-8.59	-3.69	4.90
95% CI	-14.92 to -2.25	-10.02 to 2.64	-1.51 to 11.31
p-value	0.005	0.34	0.16
EDV			
Mean difference	0.27	2.27	2.0
95% CI	-1.52 to 2.06	0.43 to 4.12	0.13 to 3.8
p-value	0.93	0.01	0.03
RI			
Mean difference	-0.10	-0.16	-0.06
95% CI	-.0.17 to -0.03	-0.23 to -0.09	-0.13 to 0.004
p-value	0.002	0.00001	0.07

in our study may be due to downstream vascular changes related to diabetes in both retinal & choroidal circulation [17].

Gracner studied blood flow velocities in 44 eyes of 44 diabetes patientsand 22 eyes of 22 age and gender matched controls of around 60 years of age. They found a significant increase (P<0.05) in the PSV of OA in the advance retinopathy group [severe nonproliferative diabetic retinopathy (SNPDR)/PDR] as compared to controls. It is likely that the changes that we found between controls and early retinopathy cases became evident in their study, only in the advanced retinopathy patients. Gracner suggests that the changes could in part be explained due to significantly higher mean blood pressure between diabetics and healthy controls. There was no significant difference in EDV and RI [16]. Mendivil in a two group design, prospectively compared vascular dynamics in PDR (n=25) and healthy controls (n=30) [8]. They found a significant decrease (p<0.01) in the PSV of OA in the PDR group (mean 31.7 cm/s) as compared to controls (36.6 cm/s). This is in contrast to our and Gracner's findings. This could be explained since in diabetes, capillaries are known to dilate [15], and altered blood rheology occurs. With an increase in blood and plasma viscosity, increased RBC aggregation and altered platelet morphology, [18-20] a reduction in blood flow is seen without autoregulation. Both vascular dilation and alteration in rheology could explain a slowing down of velocity. They reported a significant decrease in PSV and EDV in PDR as compared to controls in both CRA and OA.Mackinnon studied 17 controls and 45 diabetic patients in their study. Diabetics were further divided into NDR/BDR and PPDR/PDR group like us. They did not find a significant increase in PSV of OA, but their data in the study tends to indicate an increase in PSV in the diabetics as compared to controls. Similar to us, they also found a significantly higher RI in the OA of both the groups as compared to the normal subjects [17]. They suggested that an increased RI in the OA in both diabetic groups may be due to downstream vascular changes, e.g., diabetes associated vascular damage in both the retinal and choroidal vasculature. Measurement of OA blood flow velocity probably represents changes in choroidal blood flow. It has been estimated that of the total ocular blood supply less than 10% flows to the retina, remainder being directed to choroid via PCA. So microangiopathy due to diabetes affecting choroidal circulation affects OA flow velocity characteristics.

Numerous other authors have done similar studies but failed to detect any significant changes in the PSV of OA in diabetics as compared to controls [4,17,21-24].

Dimitrova studied choroidal circulatory changes in diabetic patients with and without DR by measuring velocity of posterior ciliary artery, CRA and OA and the respective veins in 73 diabetics and 22 controls [23]. They found significantly lower EDV (p< 0.01) in the BDR group compared with controls and NDR group. There was no significant difference in the EDV between NDR and control group, while RI was significantly higher in BDR group as compared to controls and NDR group in OA. In our study, we found higher RI in PPDR/PDR and NDR/BDR group as compared to normal controls in OA.Arai compared 22 age and gender matched normal subjects and 55 diabetic patients [22]. They showed significantly lower EDV in OA of diabetic patients regardless of presence or absence of retinopathy than those of normal subjects. EDV was also significantly lower (P<0.01) in diabetic retinopathy group as compared to non-retinopathy group. So EDV was decreased in the OA in all groups as DR progressed. An increase in RI was also reported in DR as compared to diabetics without retinopathy and normal subjects. Similarly, we too found significant decrease in the EDV and increase in RI.

Baydar studied 65 eyes of 33 diabetic patients and 22 eyes of 11 controls. They compared the results of 5 eyes with severe Nonproliferative Diabetic Retinopathy (NPDR), 8 eyes with moderate NPDR, 18 eyes with mild NPDR and 34 eyes with non-retinopathy groups to 22 control eyes as well. The RI was significantly higher (t test; p<0.05) only in moderate NPDR (0.80 ± 0.05) as compared to non-retinopathy group (0.71 ± 0.09) in OA. Rest other diabetic groups did not have significant differences [24]. Bastarkstudied only RI values in 91 type 2 diabetic patients with microalbuminuria and 27 healthy subjects. Diabetic patients were further subdivided into two groups according to presence or absence of retinopathy. There was no statistical difference in mean RIs of all three vessels between the control group and diabetics with retinopathy, although they reported a significantly higher RI in diabetic patients with retinopathy as compared to diabetics without retinopathy in the OA. Similarly, we too found significant differences but in diabetics as compared to controls only in OA. They concluded that orbital vascular resistance (RI) in diabetic patients with retinopathy is higher than diabetic patients without retinopathy and healthy subjects [25]. Also, they reported that the RI of OA ≥ 0.72 predicts the presence of diabetic retinopathy with sensitivity of 78.4 % and specificity of 70% with area under the curve of 0.849 by Receiver Operating Curve analysis (ROC). Tamaki was the first todo a case control study using color Doppler in 36 diabetic patients in OA only, and found RI to be higher in diabetics as compared to control groups [26].

We found no significant differences in PSV of CRA (ANOVA; P=0.49), on the other hand numerous other authors have found a significant decrease in those with diabetics as compared to controls [8,16,17,21-24]. Similar to us, only Arai et al found no significant difference in PSV between patients with and without diabetic retinopathy [22]. EDV is decreased in most of the studies in diabetics

as compared to normal controls [8,16,17,21-24]. While none of the studies reported increase in PSV and EDV. RI was shown to be significantly increased in diabetics in manystudies [22,23,25]. Only Baydar reported significant decrease in RI of CRA [24]. Rest all authors reported no significant differences [16,17].

Conclusion

There is conflicting data regarding changes in blood flow velocity and RI in diabetics in the literature as both reduction and increase in blood flow has been reported. This could be on account of differing changes in multiple aspect of the vessel.For instance narrowing of the lumen, per se should increase velocity of flow, while increase platelet stickiness would likely slow it. The final result would thus tend to be different depending on which factor or factors were dominating. Perhaps a meta-analysis would help clarify the debate. There are definitive hemodynamic alterations in Diabetic Retinopathy (DR) as compared to normal persons. Worsening RI in OA due to deleterious effects of diabetes irrespective of diabetic retinopathy stages can be a preclinical marker for future macrovascular events like stroke and myocardial infarction, and thus can be an area of further research. This simple marker can be a warning indicator for necessary intervention.

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