Blood Flow Parameters of the Central Retinal and Internal Carotid Arteries in Asymmetric Diabetic Retinopathy

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Purpose: To investigate the correlation between diabetic retinopathy severity and blood flow parameters in the central retinal artery (CRA) and internal carotid artery (ICA).

Methods: This comparative study included 40 eyes of 20 patients with asymmetric diabetic retinopathy. Twelve subjects had asymmetric diabetic macular edema while eight patients had proliferative diabetic retinopathy (PDR) in one eye and non-proliferative diabetic retinopathy (NPDR) in the fellow eye. Bilateral color Doppler imaging (CDI) of the CRA and ICA was performed to determine resistance index (RI) and peak systolic velocity (PSV). RI and PSV values were compared between eyes with higher grades of macular edema (> 2 grades of difference with the fellow eye) and fellow eyes with less severe macular edema, as well as between eyes with PDR and fellow eyes with NPDR.

Results: Mean RI of the CRA in eyes with higher grades of macular edema was 0.78±0.11 as compared to 0.69±0.08 in fellow eyes with less severe macular edema (P=0.012), while PSV of the CRA was 58.83±18.93 cm/s in eyes with higher grades of macular edema versus 59.75±11.83 cm/s in fellow eyes with less severe macular edema (P=1.00). Mean PSV of the ICA was 55±23.94 cm/s in eyes with PDR and 69.25±34.30 cm/s in eyes with NPDR (P=0.008) while mean RI of the ICA was 0.81±0.13 in eyes with PDR and 0.76±0.12 in eyes with NPDR (P=1.00).

Conclusion: Evaluation of RI in the CRA and PSV in the ICA by CDI in diabetic patients may identify eyes at risk of more severe macular edema and PDR.

Keywords: Color Doppler Imaging; Central Retinal Artery; Internal Carotid Artery; Diabetic Retinopathy

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of visual impairment with increasing prevalence worldwide.1 The condition results from microvascular decompensation beginning with basement membrane thickening, eventually leading to vascular occlusion and neovascularization.2,3 Diabetic macular edema (DME) is one of the most common causes of visual loss in patients with diabetes mellitus and has a poorly defined pathogenesis.4 Proliferative diabetic retinopathy (PDR) occurs in later stages of diabetic retinopathy and can lead to tractional retinal detachment and vitreous hemorrhage.5 Prevention of diabetic retinopathy is...
becoming increasingly important from a public health standpoint. There is a clear need for more effective diagnostic and therapeutic techniques to reduce the burden of this sight threatening condition.\(^6\,7\) Evaluating blood flow and physical characteristics of ocular vessels by new techniques such as color Doppler imaging (CDI) may help in early diagnosis and monitoring of this complication of diabetes. CDI allows two-dimensional structural imaging together with evaluation of blood flow even in fine vessels such as the central retinal artery (CRA).\(^8\) Vascular resistance against blood flow cannot be directly measured and is calculated by the following formula: RI=(PSV-EDV)/PSV where RI stands for resistance index, PSV is peak systolic velocity and EDV represents end diastolic velocity.

RI values vary from 0 to 1, with higher scores indicating greater vascular resistance.\(^9\) Previous studies have shown that monitoring the ophthalmic artery, CRA and short posterior ciliary arteries using CDI may have predictive value for identifying eyes at higher risk of sight threatening diabetic retinopathy.\(^10,\,11\)

The aim of this study was to evaluate the possible association between RI and PSV of the CRA and internal carotid artery (ICA) on one hand with clinically significant macular edema (CSME) and PDR on the other hand utilizing CDI in patients with asymmetric DR.

**METHODS**

This masked comparative study was performed on patients referred to Poostchi Diabetic Retinopathy Clinic, Shiraz, Iran. Twenty diabetic patients who had asymmetric diabetic retinopathy or macular edema and had not received any treatment were enrolled. The study was conducted according to the Declaration of Helsinki\(^12\) and informed consent was obtained from all participants.

Fundus examination was performed for all patients by an ophthalmologist. Clinical variables were defined as follows:

Asymmetric diabetic retinopathy: PDR in one eye and moderate or severe, but not very severe non-proliferative diabetic retinopathy (NPDR) in the fellow eye.

Asymmetric DME: Difference exceeding 2 grades (Table 1) between fellow eyes confirmed by optical coherence tomography (OCT).

CSME: Defined according to the Early Treatment Diabetic Retinopathy Study (EDTRS) definitions.\(^13,\,14\)

Patients with other retinal pathologies leading to asymmetric retinopathy, such as asymmetric intraocular pressure, unilateral optic atrophy, high myopia, colobomas, chorioretinal scars, previous laser therapy, and intraocular surgery or injections were excluded from the study.

CDI was performed by an experienced sonographist with the LOGIQ 500 device (General Electric, Tokyo, Japan) using two transducers; one for B-mode with 7.0 MHz frequency (depth of penetration was 40 mW/cm\(^2\)), and the other one for pulsed Doppler with 5 MHz frequency (depth of penetration was 25 mW/cm\(^2\)). The patient was examined in supine position and the depth of ultrasound penetration was set at 40 mm. The probe was placed on the closed upper eyelid following application of sterile contact gel to minimize the force of the probe on the globe. Blood flow velocity in the CRA was measured within the least echogenic optic nerve shadow, 1-2 mm posterior to the globe. PSV and EDV were measured and RI was calculated. CDI was also performed to determine PSV and RI in both ICAs.

Statistical analysis was performed using SPSS software version 16. Mean RI and PSV values were compared between eyes with higher grades of DME and fellow eyes with less severe DME, as well as between eyes with PDR and fellow eyes with NPDR using Mann-Whitney U-test; P values <0.05 were considered as significant.

| Grading | CSME | CMT (µm) |
|---------|------|----------|
| 1 +     | Absent | ≤ 300    |
| 2 +     | Present | 300-400  |
| 3 +     | Present | 400-500  |
| 4 +     | Present | ≥ 500    |

CSME, clinically significant macular edema  
CMT, central macular thickness
RESULTS

Of 20 patients with asymmetric diabetic retinopathy, 12 subjects (group A) had an inter-eye difference in DME exceeding 2 grades and 8 individuals (group B) had PDR in one eye and NPDR in the fellow eye. In group A, DME was more severe in the right and left eyes, each in 6 patients. In group B, 5 patients had PDR in the right eye and 3 cases had PDR in the left eye. CDI parameters and retinal findings of these two subgroups are compared in Tables 2 and 3.

Mean RI of the CRA was significantly greater in eyes with higher grades of DME as compared to eyes with less severe DME (0.78±0.11 vs 0.69±0.08; P=0.012) but mean PSV of the ICA was not significantly different (58.83±18.93 cm/s and 59.75±11.83 cm/s, respectively; P=1.00). On the other hand, mean PSV of the ICA was significantly lower in eyes with PDR as compared to eyes with NPDR (55±23.94 cm/s vs 69.25±34.30 cm/s, P=0.008) but mean RI of the CRA was not significantly different (0.81±0.13 and 0.76±0.12, respectively; P=1.00).

DISCUSSION

The exact nature of ocular blood flow abnormalities in different stages of diabetic retinopathy is a matter of controversy. Retinal vasodilatation and an increase in retinal blood flow have been suggested to eventually lead to development of diabetic retinopathy, possibly because of increased frictional forces (i.e., shear stress) on the endothelial lining of retinal vessels. Some studies have reported variable fluctuations in retinal blood flow in patients with diabetes mellitus as compared to normal subjects. However, an increase in retinal blood flow has not been supported by other studies; Grunwald et al found no significant difference in retinal blood flow between diabetic and non-diabetic individuals.

Understanding the ocular circulation in diabetics requires analysis of retrobulbar, CRA and ophthalmic artery hemodynamics. Goebel et al found considerably lower PSV and EDV values in the CRA of patients with untreated diabetic retinopathy compared as to normal controls. However, Dimitrova et al demonstrated that circulatory parameters such as PSV, EDV, and RI in the CRA and posterior ciliary artery were not significantly different among diabetics during progression of diabetic retinopathy. In another study, Guven et al showed that maximum blood flow levels of the CRA were significantly higher in pre-retinopathic eyes as compared to NPDR eyes. Mendivil et al concluded that ocular blood flow parameters such as systolic, diastolic and mean velocity of the ophthalmic artery and

| Table 2. Color Doppler imaging parameters and retinal findings in group A |
|---------------------------|-------------------|-------------------|
| Patients | CRA-RI | ICA-PSV (cm/s) | DME |
| Left | Right | Left | Right | Left | Right |
| 1 | 0.67 | 0.61 | 55 | 56 | +1 | +4 |
| 2 | 0.68 | 0.69 | 51 | 58 | +4 | +1 |
| 3 | 0.76 | 0.58 | 52 | 42 | +1 | +4 |
| 4 | 0.71 | 0.65 | 78 | 89 | +1 | +4 |
| 5 | 0.86 | 0.79 | 54 | 68 | +2 | +4 |
| 6 | 0.74 | 1.01 | 101 | 83 | +4 | +1 |
| 7 | 0.66 | 0.69 | 57 | 50 | +4 | +2 |
| 8 | 0.64 | 0.58 | 34 | 57 | +4 | +2 |
| 9 | 0.69 | 0.75 | 51 | 74 | +4 | +2 |
| 10 | 0.65 | 0.77 | 55 | 57 | +4 | +1 |
| 11 | 0.70 | 0.70 | 53 | 50 | +2 | +4 |
| 12 | 0.77 | 0.74 | 46 | 52 | +2 | +4 |

CRA, central retinal artery; ICA, internal carotid artery
RI, resistance index; PSV, peak systolic velocity
DME, diabetic macular edema

| Table 3. Color Doppler imaging parameters and retinal findings in group B |
|---------------------------|-------------------|-------------------|
| Patients | CRA-RI | ICA-PSV (cm/s) | Retinal findings |
| Left | Right | Left | Right | Left | Right |
| 1 | 0.82 | 0.80 | 150 | 112 | NPDR | PDR |
| 2 | 0.67 | 0.67 | 48 | 67 | PDR | NPDR |
| 3 | 0.69 | 0.68 | 43 | 51 | NPDR | ME+4 |
| 4 | 1.0 | 1.0 | 38 | 47 | PDR | ME+3 |
| 5 | 0.87 | 0.82 | 57 | 50 | NPDR | ME+4 |
| 6 | 0.69 | 0.98 | 56 | 60 | PDR | ME+3 |
| 7 | 0.80 | 0.80 | 54 | 77 | PDR | NPDR |
| 8 | 0.69 | 0.70 | 45 | 39 | NPDR | ME+4 |

CRA, central retinal artery; ICA, internal carotid artery
RI, resistance index; PSV, peak systolic velocity
NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ME, macular edema
CRA in patients with PDR was significantly lower compared to healthy subjects. Some other studies revealed that blood flow decreased with insulin treatment but increased with advancing retinopathy.\textsuperscript{10,22} Kawagishi et al\textsuperscript{23} found an increase in RI in the CRA of patients with type 1 diabetes mellitus prior to the development of retinopathy.

The results of our study demonstrate that RI of the CRA is higher in eyes with more severe DME, however there was no significant correlation between the presence of PDR and RI of the CRA. Capillary occlusion as a result of diabetic retinopathy is the probable cause of increased RI; however, hyperperfusion in the remaining capillary plexus, especially in the perifoveal area leads to intraretinal fluid accumulation and hemorrhage, and eventually DME in this area. With the evolution of new vessels, these shunt vessels cause reduction in RI to the level of the other eye or even less, however these abnormal vessels cannot compensate for retinal ischemia, thus PDR will progress.

In our study, patients with PDR in one eye had lower PSV in the ipsilateral ICA. Interestingly, the right eye was more frequently involved. Higher PSV in the left ICA might be due to its direct origin from the aorta as compared to indirect branching of the right ICA from the aorta via the brachiocephalic artery. Lower perfusion pressure on the right side might lead to higher rates of ischemic events in the retina and higher rates of PDR in the ipsilateral eye. We postulate that reduction of PSV and retinal blood flow in the diabetic eye can cause progression to proliferative retinopathy.

The role of ICA blood flow on development and progression of diabetic retinopathy has remained controversial.\textsuperscript{16,24} In some studies, mild to moderate stenosis of the ipsilateral ICA has been mentioned as a preventive factor for diabetic retinopathy, while severe stenosis was associated with more severe diabetic retinopathy.\textsuperscript{16,24,25}

It might be concluded that measuring RI of the CRA in diabetic patients may help earlier recognition of eyes susceptible to DME leading to timely diagnosis and treatment. CDI in diabetic patients can also help detect subjects at higher risk of PDR by measuring PSV in the ICA. Our study is limited by the small sample size, therefore larger studies are required to confirm these observations.

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**Conflicts of Interest**

None.

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