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Doppler ocular ultrasound in patients with type 2 diabetes mellitus

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Purpose: *To determine ocular blood flow parameters by Doppler ultrasound scanning in type 2 diabetic patients with different stages of diabetic retinopathy.*

Material and Methods: *In this prospective study, forty-five patients (90 eyes) with type 2 diabetes mellitus were divided into three groups of 15 patients each: no diabetic retinopathy group (DR0), non-proliferative retinopathy (NPDR), and proliferative retinopathy (PDR) groups. Doppler indices such as systolic blood flow velocity (Vs), diastolic blood flow velocity (Vd), time-averaged maximum velocity (TAMXV), pulsatility index (PI) and resistivity index (RI) in the ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary arteries (SPCA) were determined. ANOVA was used for quantitative comparisons between the three groups.*

Results: *There was a significant ($p < 0.05$) decrease in (a) the Vs from 71.1 ± 20.6 cm/s in the DR0 group to 59.9 ± 16.7 cm/s in the NPDR group and 47.4 ± 16.4 cm/s in the PDR group, (b) Vd from 22.1 ± 6.9 cm/s to 17.0 ± 6.6 cm/s and 12.3 ± 5.9 cm/s, respectively; and (c) TAMXV from 37.2 ± 11.3 cm/s to 31.9 ± 9.1 cm/s and 25.3 ± 9.7 cm/s, respectively, and an increase in the RI from 0.69 ± 0.06 cm/s to 0.71 ± 0.09 cm/s and 0.75 ± 0.08 cm/s, respectively, in the OA. In addition, there was a significant decrease in the Vd from 9.9 ± 5.4 cm/s in the DR0 group to 8.1 ± 3.8 cm/s in the NPDR group and 5.5 ± 3.1 cm/s in the PDR group, and an increase in the PI from 1.34 ± 0.16 cm/s to 1.46 ± 0.28 cm/s and 1.54 ± 0.24 cm/s, respectively, and in the RI from 0.71 ± 0.06 cm/s to 0.75 ± 0.07 cm/s and 0.80 ± 0.05 cm/s, respectively, in the CRA. Moreover, there was a significant decrease in the Vd from 4.3 ± 1.6 cm/s in the DR0 group to 3.2 ± 2.0 cm/s in the NPDR group and 3.1 ± 2.2 cm/s in the PDR group, and an increase in the PI from 1.32 ± 0.21 cm/s to 1.37 ± 0.24 cm/s and 1.54 ± 0.26 cm/s, respectively, and in the RI from 0.76 ± 0.04 cm/s to 0.82 ± 0.06 cm/s and 0.82 ± 0.06 cm/s, respectively, in the SPCA.*

Conclusion: *We found that the arteries examined in patients with diabetic retinopathy tended to have decreased blood flow velocities and increased resistivity and pulsatility indices, with the greatest changes observed in patients with PDR. In addition, the difference in mean values of most Doppler indices between the PDR and NPDR groups was larger than that between the NPDR and DR0 groups.*

Keywords:

type 2 diabetes mellitus, diabetic retinopathy, Doppler ultrasound, central retinal artery, ophthalmic artery, short posterior ciliary arteries

Introduction

The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrates, fat, protein metabolism resulting from defects in insulin secretion, insulin action or both. DM is a multifactorial disease, with major contributions from genetic factors, environmental factors and way of life.[1]

Diabetic complications result from the development of diabetic angiopathy, a generalized lesion of the blood vessels involving both the small vessels (microangiopathy) and those of a medium and large size (macroangiopathy). Metabolic, hemodynamic and hemorheologic factors are believed to be the best studied factors causing the development and progression of diabetic angiopathy. These mechanisms are interrelated and tend to interact, eventually causing the evolution of diabetic angiopathy.[2, 3, 4, 5, 6]

Microangiopathies and macroangiopathies cause lesions in a number of target organs and the development of diabetic nephropathy, retinopathy and neuropathy.[7,8] Diabetic retinopathy is a common complication among elderly diabetic patients in the developed world and a leading cause of blindness and vision impairment; approximately 75% of persons suffering from type 1 DM develop retinopathy, while approximately 50% of persons with type 2 DM may develop retinopathy. Other microvascular lesions are a significant risk factor for such potentially life-threatening complications as heart attacks, stroke, etc.[9, 10, 11] Given that abnormalities in retinal hemodynamics

are involved in the pathogenesis of diabetic retinopathy, a better understanding of the changes in retinal blood flow would give insights into the pathophysiology of the disease and would help identify potentially beneficial therapy for prevention of diabetic retinopathy.[12]

The introduction of orbital color Doppler imaging (CDI) in 1989 [13] presented the opportunity for assessment of orbital blood vessels. CDI is a non-invasive ultrasonic method for qualitatively and quantitatively assessing blood flow velocity information [14, 15]. Good reproducibility of measurements in the ophthalmic and central retinal arteries has been reported.[16] Simultaneous Doppler information is gathered from a cross-section of tissue combined with B-scan recording. Pulsatile blood velocity profiles are then obtained and analyzed.[17] At present, CDI is the first-line examination in the assessment of retrobulbar circulation. Doppler imaging is based on the Doppler principle: a probe emits ultrasound waves which are reflected by moving blood cells within vessels, with these cells either increasing or decreasing the frequency of the reflected waves depending on the direction of the blood flow. Thus, the direction and the velocity of the blood flow can be calculated. The direction of blood flow is than translated into a color scale on the ultrasound image. According to convention, flow towards the probe is depicted in red, representing arterial blood, while flow away from the probe is depicted in blue, representing venous blood. Test/retest reproducibility of CDI assessment of blood flow velocity in orbital vessels is at least reasonable but variation in reproducibility depends upon examination technique and operator skills. The variability of measurements of the peak systolic velocity (PSV) and end diastolic velocity (EDV) is rather high and higher than that of measurements of the resistivity index (RI).[18]

The purpose of the study was to determine ocular blood flow parameters by Doppler ultrasound scanning in type 2 diabetic patients with different stages of diabetic retinopathy.

Material and Methods

Forty-five patients (90 eyes; 13 men and 22 women) with type 2 diabetes mellitus who were treated on inpatient basis at the Endocrinological Department of Dnipropetrovsk Regional Clinical Hospital, and examined at the diabetic retinopathy room of Dnipropetrovsk Regional Clinical Eye Hospital, were included in this prospective cohort study. Patients were divided into three groups based as per the International Council of Ophthalmology (ICO) criteria [19]: group 1 or no diabetic retinopathy group (DR0), group 2 or non-proliferative retinopathy (NPDR) group, and group 3 or proliferative retinopathy (PDR) group. The same retinopathy stage in both eyes of one subject was required. Patients with a history of acute impairment of retinal blood flow (central retinal artery occlusion and thrombosis of the central retinal vein or branch retinal vein), patients with glaucoma, vitreous hemorrhage, non-transparent media, and patients with a history of panretinal laser coagulation or vitreoretinal surgery were excluded.

All study patients had endocrinologic evidence of optimal glycemic control or suboptimal control at the time of examination. If indicated, patients were receiving hypotensive medications and means for coagulogram and lipidogram monitoring in addition to hypoglycemic therapy.

A general clinical eye examination (visual acuity, tonometry, and binocular ophthalmoscopy) and auxiliary eye examination (fundus photography, optical coherence tomography and ultrasound B scanning) were used to determine the presence of diabetic retinopathy.

A Katena Diamond 90D non-contact lens and a Shin Nippon SL-45 slit lamp were used to perform fundus ophthalmoscopy, a Carl Zeiss Visucam 524 fundus camera, to perform fundus photography, an Optovue RT Vue 100-2 apparatus (Optovue Inc., Fremont, CA, USA) to perform spectral-domain optical coherence tomography, and a Quantel Medical Compact-II ultrasound system (Quantel medical, Clermont-Ferrand, France), to perform an ultrasound study.

Doppler ultrasound scanning of ophthalmic vessels included an examination of blood flow in the ophthalmic artery, central retinal artery and short posterior ciliary arteries with the use of a General Electric Logiq 3 Expert scanner with a 10-MHz probe. Systolic blood flow velocity (Vs), diastolic blood flow velocity (Vd), time-averaged maximum velocity (TAMXV), pulsatility index (PI = Vs-Vd/Vmean) and resistivity index (RI = Vs-Vd/Vs) of the examined vessels were determined.

The study was approved by the Biomedical Ethics Committee of the Dnipro State Medical University. Informed consent was obtained prior to participation.

Statistica v6.1 (Statsoft, Tulsa, OK; № AGAR909E-415822FA) software was used for statistical analysis.

Mean and standard deviation (SD) values were calculated to compare normally distributed quantitative variables. Independent sample Student t-test was used for quantitative comparisons between two groups and parametric analysis of variance (ANOVA) for quantitative comparisons between three groups. Contingency tables and Pearson Chi-Square statistics were used for qualitative comparisons between groups, with Pearson's $\chi 2$ test with Yates' continuity correction used for the difference values close to zero. The level of significance $p < 0.05$ was assumed.

Results

Mean age plus or minus standard deviation was 62.1 ± 6.5 years for the DR0 group, 60.3 ± 7.3 years for the NPDR group, and 63.9 ± 7.2 років years for the PDR group ($p > 0.05$). There was also no statistical difference in the distribution of patients by sex between the groups ($p > 0.05$), and the percentages of men and of women were 53.3% and 46.7% for the DR0 group, 40.0% and 60.0% for the NPDR group, and 60.0% and 40.0% for the PDR group (Table 1).

Table 2 shows the results of Doppler ultrasound scanning of ophthalmic vessels for the three groups of patients. The ophthalmic artery, central retinal artery and short posterior ciliary arteries in patients with diabetic retinopathy tended to have decreased peak systolic and diastolic velocities and time-averaged maximum velocity, with the greatest changes observed in patients with proliferative diabetic retinopathy. In addition, pulsatility index and resistivity index were high for these vessels in patients with NPDR or PDR.

It is of note that the changes in ophthalmic artery RI and central retinal artery and short posterior ciliary arteries Vs and TAMXV were not statistically significant ($p>0.05$).

Tables 3 to 5 show the results of pairwise group comparisons for Doppler indices, with the significance of differences in variables between groups indicated. The differences in mean values of most Doppler indices between the NPDR and PDR groups were greater than the differences between the DR0 and NPDR groups.

Discussion

CDI has made it possible to evaluate orbital blood flow under real time and physiological conditions. In addition, unlike fluorescein angiography, it is noninvasive. Moreover, laser Doppler velocimetry, but not CDI, requires transparent ocular media. The CDI technology allows the

Table 1. Age and sex characteristics of the total study sample and no retinopathy (DR0), non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) groups

Characteristics	Total study sample (n = 45)	Clinical groups			Statistical significance of difference between groups (P-value)
		DR0 (n = 15)	NPDR (n = 15)	PDR (n = 15)	
Years of age, mean ± SD	63.3 ± 9.3	62.1 ± 6.5	60.3 ± 7.3	63.9 ± 7.2	0.381*
Sex, number/ percentage:					
men	23 / 51.1	8 / 53.3	6 / 40.0	9 / 60.0	0.537**
women	22 / 48.9	7 / 46.7	9 / 60.0	6 / 40.0	

Note: *, as assessed by parametric analysis of variance (ANOVA); **, as assessed by χ^2.

Table 2. Doppler indices of the ophthalmic artery, central retinal artery and short posterior ciliary arteries in no retinopathy (DR0), non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) groups

Index (mean ± SD)	Clinical groups			Statistical significance of difference between groups (P-value)*
	DR0	NPDR	PDR	
Ophthalmic artery				
Vs (cm/s)	71.1 ± 20.6	59.9 ± 16.7	47.4 ± 16.4	0.000
Vd (cm/s)	22.1 ± 6.9	17.0 ± 6.6	12.3 ± 5.9	0.000
TAMXV (cm/s)	37.2 ± 11.3	31.9 ± 9.1	25.3 ± 9.7	0.000
PI	1.33 ± 0.19	1.39 ± 0.41	1.42 ± 0.22	0.531
RI	0.69 ± 0.06	0.71 ± 0.09	0.75 ± 0.08	0.008
Central retinal artery				
Vs (cm/s)	33.0 ± 13.0	34.5 ± 18.0	27.3 ± 13.9	0.155
Vd (cm/s)	9.9 ± 5.4	8.1 ± 3.8	5.5 ± 3.1	0.001
TAMXV (cm/s)	17.7 ± 8.2	17.5 ± 8.2	14.3 ± 7.6	0.186
PI	1.34 ± 0.16	1.46 ± 0.28	1.54 ± 0.24	0.006
RI	0.71 ± 0.06	0.75 ± 0.07	0.80 ± 0.05	0.000
Short posterior ciliary arteries				
Vs (cm/s)	18.1 ± 6.3	17.2 ± 7.6	15.6 ± 7.1	0.393
Vd (cm/s)	4.3 ± 1.6	3.2 ± 2.0	3.1 ± 2.2	0.026
TAMXV (cm/s)	10.4 ± 3.1	10.3 ± 4.2	8.5 ± 3.9	0.095
PI	1.32 ± 0.21	1.37 ± 0.24	1.54 ± 0.26	0.002
RI	0.76 ± 0.04	0.82 ± 0.07	0.82 ± 0.06	0.000

Note: *, as assessed by parametric analysis of variance (ANOVA)

Table 3. Pairwise comparison of the no retinopathy (DR0) and non-proliferative diabetic retinopathy (NPDR) groups for Doppler indices of the ophthalmic artery, central retinal artery and short posterior ciliary arteries

Index (mean ± SD)	Clinical groups			Statistical significance of difference between groups (P-value)*
	DR0	NPDR	Difference of mean values	
Ophthalmic artery				
Vs (cm/s)	71.1 ± 20.6	59.9 ± 16.7	11.2	0.024
Vd (cm/s)	22.1 ± 6.9	17.0 ± 6.6	5.1	0.005
TAMXV (cm/s)	37.2 ± 11.3	31.9 ± 9.1	5.3	0.050
PI	1.33 ± 0.19	1.39 ± 0.41	0.06	0.498
RI	0.69 ± 0.06	0.71±0.09	0.02	0.133
Central retinal artery				
Vs (cm/s)	33.0 ±1 3.0	34.5 ± 18.0	1.5	0.713
Vd (cm/s)	9.9 ± 5.4	8.1 ± 3.8	1.8	0.158
TAMXV (cm/s)	17.7 ± 8.2	17.5 ± 8.2	0.2	0.900
PI	1.34 ± 0.16	1.46 ± 0.28	0.06	0.048
RI	0.71 ± 0.06	0.75 ± 0.07	0.04	0.010
Short posterior ciliary arteries				
Vs (cm/s)	18.1 ± 6.3	17.2 ± 7.6	0.9	0.620
Vd (cm/s)	4.3 ± 1.6	3.2 ± 2.0	1.1	0.016
TAMXV (cm/s)	10.4 ± 3.1	10.3 ± 4.2	0.1	0.917
PI	1.32 ± 0.21	1.37 ± 0.24	0.05	0.389
RI	0.76 ± 0.04	0.82 ± 0.07	0.06	0.000

Note: *, as assessed by the Student t-test

Table 4. Pairwise comparison of the non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) groups for Doppler indices of the ophthalmic artery, central retinal artery and short posterior ciliary arteries

Index (mean ± SD)	Clinical groups			Statistical significance of difference between groups (P-value)*
	NPDR	PDR	Difference of mean values	
Ophthalmic artery				
Vs (cm/s)	59.9 ± 16.7	47.4 ± 16.4	12.5	0.006
Vd (cm/s)	17.0 ± 6.6	12.3 ± 5.9	4.7	0.005
TAMXV (cm/s)	31.9 ± 9.1	25.3 ± 9.7	6.6	0.009
PI	1.39 ± 0.41	1.42 ± 0.22	0.03	0.759
RI	0.71 ± 0.09	0.75 ± 0.08	0.04	0.127
Central retinal artery				
Vs (cm/s)	34.5 ± 18.0	27.3 ± 13.9	7.2	0.087
Vd (cm/s)	8.1 ± 3.8	5.5 ± 3.1	2.6	0.005
TAMXV (cm/s)	17.5 ± 8.2	14.3 ± 7.6	3.2	0.126
PI	1.46 ± 0.28	1.54 ± 0.24	0.08	0.258
RI	0.75 ± 0.07	0.80 ± 0.05	0.05	0.002
Short posterior ciliary arteries				
Vs (cm/s)	17.2 ± 7.6	15.6 ± 7.1	1.6	0.414
Vd (cm/s)	3.2 ± 2.0	3.1 ± 2.2	0.1	0.902
TAMXV (cm/s)	10.3 ± 4.2	8.5 ± 3.9	1.8	0.091
PI	1.37 ± 0.24	1.54 ± 0.26	0.17	0.013
RI	0.82 ± 0.07	0.82 ± 0.06	0	0.972

Note: *, as assessed by the Student t-test

Table 5. Pairwise comparison of the no diabetic retinopathy (DR0) and proliferative diabetic retinopathy (PDR) groups for Doppler indices of the ophthalmic artery, central retinal artery and short posterior ciliary arteries

Index (mean ± SD)	Clinical groups			Statistical significance of difference between groups (P-value)*
	DR0	NPDR	Difference of mean values	
Ophthalmic artery				
Vs (cm/s)	71.1 ± 20.6	47.4 ± 16.4	23.7	0.000
Vd (cm/s)	22.1 ± 6.9	12.3 ± 5.9	9.8	0.000
TAMXV (cm/s)	37.2 ± 11.3	25.3 ± 9.7	11.9	0.000
PI	1.33 ± 0.19	1.42 ± 0.22	0.09	0.122
RI	0.69 ± 0.06	0.75 ± 0.08	0.06	0.001
Central retinal artery				
Vs (cm/s)	33.0 ± 13.0	27.3 ± 13.9	5.7	0.105
Vd (cm/s)	9.9 ± 5.4	5.5 ± 3.1	4.4	0.000
TAMXV (cm/s)	17.7 ± 8.2	14.3 ± 7.6	3.4	0.097
PI	1.34 ± 0.16	1.54 ± 0.24	0.2	0.000
RI	0.71 ± 0.06	0.80 ± 0.05	0.09	0.000
Short posterior ciliary arteries				
Vs (cm/s)	18.1 ± 6.3	15.6 ± 7.1	2.5	0.162
Vd (cm/s)	4.3 ± 1.6	3.1 ± 2.2	1.2	0.015
TAMXV (cm/s)	10.4 ± 3.1	8.5 ± 3.9	1.9	0.040
PI	1.32 ± 0.21	1.54 ± 0.26	0.22	0.001
RI	0.76 ± 0.04	0.82 ± 0.06	0.06	0.000

Note: *, as assessed by the Student t-test

examination, with minimal discomfort and risk, of blood flow in the orbit.[20]

The findings of the current study are in agreement with the findings of most other workers who determined Doppler indices in the vessels of the eye and orbit of diabetics.

In a study by Goebel and colleagues [21], systolic blood flow velocity was lower in proliferative eyes than in the control group (patients without diabetes) or in non-proliferative eyes. In the preproliferative group, there was great variability in velocity distribution. Consequently, no statistically significant difference could be deduced, either in the group with background retinopathy or in the group with proliferative diabetes.[21]

Kawagishi and colleagues [12] reported that PSV, EDV, and time-averaged flow velocity (TAV) were significantly lower and the RI was significantly higher in insulin-dependent DM patients without retinopathy compared to controls. They also noted that the RI was significantly correlated with plasma levels of glucose in the aforementioned patients.

Studies by Mendivil and colleagues [20] and Mendivil [22] confirmed significantly decreased blood flow velocity in the central retinal artery and ophthalmic artery but did not find significant blood flow alterations in ciliary arteries in types 1 and 2 diabetics with PDR compared to healthy controls. They also noted a significant impact of retinal laser coagulation on decreased blood flow in the central retinal artery, ophthalmic artery and ciliary arteries.

In a study by MacKinnon and colleagues [17], there was a statistically significant decrease in both the PSV and EDV of the central retinal artery in the pre-proliferative/PDR group compared to the no retinopathy/NPDR group. They also found that the RI of the ophthalmic artery was significantly increased in both the preproliferative/PDR and the no retinopathy/NPDR group compared to controls.

However, no significant differences were determined between patients with preproliferative DR and those with PDR in terms of Doppler indices for the central retinal artery and ophthalmic artery.[17]

Dimitrova and colleagues [23] investigated retrobulbar circulatory parameters in type 2 diabetic patients with and without DR progression. Eighteen patients who developed retinopathy progression showed significantly increased central retinal vein PSV, EDV and RI at the final measurement (21 months) compared to the initial measurement. Circulatory parameters in the central retinal artery and the posterior ciliary artery did not alter significantly after progression of diabetic retinopathy.

Pemp and colleagues [24] aimed to compare the diameter of the central retinal artery (CRA) between 16 type 1 diabetics with no or mild retinopathy and 16 healthy subjects. The CRA diameters were calculated from retinal

hemodynamic parameters measured with CDI and laser Doppler velocimetry. Calculated CRA diameters were significantly larger in patients with diabetes compared with healthy controls. No significant differences were found in retinal blood flow, retinal artery or vein diameters or mean flow velocity of the CRA.

It is if note that in some of the aforementioned studies, study samples included patients with both type 1 and type 2 DM. In addition, some of the aforementioned studies provided no details on the blood pressure, use of hypotensive therapy, history of previous eye surgeries, and intraocular pressure values for the patients included. Although the authors noted that the results significantly depended on the stage of diabetic retinopathy, some of the studies reported that there was no significant difference in Doppler indices of particular arteries between eyes with PDR and eyes with NPDR. [21, 12, 20, 22, 17, 24]

Moreover, blood flow velocity measurements in retrobulbar vessels using CDI need to be interpreted with caution in terms of retinal blood flow [24], and the clinical features of a particular patient should be take into account.

Conclusion

We found that the ophthalmic artery, central retinal artery and short posterior ciliary arteries in patients with diabetic retinopathy tended to have decreased peak systolic and diastolic velocities and time-averaged maximum velocity and increased resistivity and pulsatility indices, with the greatest changes observed in patients with PDR. In addition, the difference in mean values of most Doppler indices between the PDR and NPDR groups was larger than the difference between the NPDR and DR0 groups.

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