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Influence of hypertension and type 2 diabetes mellitus on cerebrovascular reactivity in diabetics with retinopathy

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BACKGROUND AND OBJECTIVES: Cerebrovascular reactivity (CVR) provides information on the intracerebral arterioles capacity to react to vasodilatory stimuli. The current study aimed to investigate the influence of hypertension and type 2 diabetes mellitus on CVR in diabetics with retinopathy.
DESIGN AND SETTING: Retrospective analysis of data prospectively collected over a 1-year period.
SUBJECTS AND METHODS: Subjects were classified into four groups each comprised of 30 participants: diabetic retinopathy with hypertension (DRH), diabetic retinopathy without hypertension (DR), hypertension without diabetes mellitus (H), and healthy controls without diabetes and hypertension (C). CVR was estimated in relation to the increase in the mean flow velocity compared with the basal velocity in both middle cerebral arteries during hypercapnia.
RESULTS: In the DRH group, the mean (SD) increase in CVR was 8.8 (2.49) cm/s, in the H group 14.4 (2.59) cm/s and in the DR group 9.7 (2.97) cm/s. The analysis of variance showed significant differences among the groups in blood flow velocity after a breath-holding test ($F=89.83$; $df=3.116$; $P<.001$).
CONCLUSIONS: Diabetes mellitus influences CVR more than hypertension.

Cerebrovascular reactivity (CVR) is a hemodynamic parameter representing the increase in normal cerebral artery blood flow in response to a vasodilatory stimulus such as hypercapnia.[1] Patients with hypertension had lower regional cerebral blood flow than normotensive patients.[2] When compared to healthy controls hypertensive individuals had decreased CVR.[3] Patients with diabetic retinopathy had significantly lower diastolic and mean flow velocites (MFV).[4] The presence of retinopathy was associated with abnormal CVR.[5] Hypertension and diabetes mellitus are considered a very strong risk factors for stroke.[6,7] The current study aims to investigate the influence of hypertension and type 2 diabetes mellitus on CVR in diabetics with retinopathy.

SUBJECTS AND METHODS

The study was approved by the local research ethical committees and written informed consent was obtained from all participants before they entered the study. Subjects were classified into four groups each comprised of 30 men: diabetic retinopathy with hypertension (DRH), diabetic retinopathy without hypertension (DR), hypertension without diabetes mellitus (H), and healthy controls without diabetes and hypertension (C). Participants were between 45 and 65 years old. Smokers were excluded. All patients and controls underwent screening for factors favoring cerebrovascular remodeling such as: systolic blood pressure, diastolic blood pressure, HbA1c, lipid profile, C-reactive protein. Blood samples were taken after an overnight fasting and routine laboratory parameters (HbA1c, C-reactive protein, cholesterol, triglyceride, HDL, and LDL- cholesterol) were determined by methods used by routine automated clinical chemistry laboratory systems. All subjects were examined by an ophthal-

mologist, neurologist and diabetologist. Patients were defined as having diabetes mellitus if their medical records showed a diagnosis of type 2 diabetes and current medical treatment with antidiabetic therapy such as diet and oral or insulin therapy. Hypertension was defined as a physician diagnosis of hypertension on treatment. Duration of disease was defined as the duration from the start of medical treatment. Duration of hypertension and diabetes mellitus was more than 10 years. Those with hemodynamically significant stenosis of the common and internal carotid arteries, the history of the cerebrovascular disease and dyslipidemia did not enter the study. We screened 220 potential subjects, but finally a total of 120 subjects met the entry criteria. Evaluation of extracranial blood vessels was performed by the color Doppler flow imaging and power Doppler imaging methods on an ATL HDI 3000 (Bothell, WA-USA), 7.5 MHz linear probe. The transcranial Doppler ultrasound examination was performed on a MultiDop L2 (DWL Electronische Systeme GmbH, Sipplingen, Germany), with a 2-MHz hand-held pulsed wave Doppler probe in supine position after 5-minute bed rest. The probe was placed over the transtemporal window. Each middle cerebral artery (MCA) was examined separately by evaluating the MFV at rest (normal respiration). CVR was assessed during the BHT as follows: the subject breathed normally by inhaling the air in the examination room and then held breath for 30 seconds. The MFV was monitored for each subject in both MCAs at rest (normal respiration - normocapnia) and at the end of the breath-holding test (BHT) when the flow velocities reached their maximal values (hypercapnia). CVR was estimated in relation to the increase in the MFV in both MCAs during hypercapnia compared with the basal velocity in cm/s.

Normality of continuous variables distributions was tested with the Shapiro-Wilk test, and homogeneity of variances with the Levene test. Differences in clinical characteristics between groups were tested by the Kruskal-Wallis test. Comparison of the CVR parameters was performed using ANOVA tests. Tukey HSD test was made after significant ANOVA results. Correlation between variables was measured with Pearson correlation coefficient. A $P<.05$ was accepted as a level of significant difference.

RESULTS

The participation was voluntary and amongst the 220 subjects finally, 120 completed the trial. The most relevant clinical and laboratory parameters of participants are summarised in **Table 1**. After the Kruskal-Wallis test was performed there was statistically significant difference between groups in their age ($\chi^2=8.14$; ss=3; $P=.043$; $\eta^2=0.07$), duration of disease ($\chi^2=14.578$; ss=2;$P<.001$; $\eta^2=0.16$), BMI ($\chi^2=11.24$; ss=3; $P=.010$; $\eta^2=0.09$), SBP ($\chi^2=79.78$; ss=3; $P<.001$; $\eta^2=0.67$), DBP ($\chi^2=77.07$; ss=3; $P<.001$; $\eta^2=0.65$) and HbA1c ($\chi^2=79.67$; ss=3; $P<.001$; $\eta^2=0.67$). The value of CRP did not differ significantly ($P=.368$).The results of absolute blood flow velocities in our participants are expressed in **Table 2**. Control group MFV difference was significantly higher than that in DRH, DR, and the H group ($P<.001$). The hypertensive group had significantly higher MFV difference than DRH and DR groups ($P<.001$). There was no significant MFV difference between DRH and DR group ($P=.643$). Cerebrovascular reactivity expressed as difference of MFV was correlated with clinical and laboratory parameters of participants

Table 1. Clinical characteristics and laboratory parameters of participants.

	Group - DRH	Group - DR	Group - H	Group - C
Age (years)	59 (52.8-61.0)	56 (50.0-61.0)	60 (55.8-62.0)	55 (51.0-59.8)
Duration of disease (H or DM) (years)	17 (11.8-24.0)	16 (12.8-21.0)	12 (10.0-14.0)	NA
BMI (kg/m^2)	27.9 (25.34-29.88)	29.1 (26.73-30.86)	28.3 (25.78-29.66)	25.9 (24.38-28.01)
SBP (mmHg)	150 (140.0-152.5)	123 (120.0-130.0)	140 (138.8-150.0)	120 (110.0-120.0)
DBP (mmHg)	95 (90.0-100.0)	80 (73.8-85.0)	90 (90.0-95.0)	78 (70.0-80.0)
HbA1c (%)	7.6 (6.37-9.76)	7.2(6.77-8.31)	5.2 (4.89-5.63)	5.4 (4.80-5.63)
CRP (mmol/L)	3.8 (2.10-6.58)	4.8 (4.08-6.53)	3.6 (2.15-6.45)	4.3 (2.38-5.23)

Data are median (range)

H, hypertension; DM,diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; DRH, diabetic retinopathy with hypertension; DR, diabetic retinopathy without hypertension; C, healthy controls; NA, not applicable

Table 2. Mean blood flow velocities in the middle cerebral artery.

Value	Group - DRH	Group - DR	Group - H	Group - C
MFV basal (cm/s)	57.4 (10.33)	57.7 (8.54)	57.1 (8.61)	58.2 (8.78)
MFV after BHT (cm/s)	66.1 (10.54)	67.3 (8.06)	71.5 (9.68)	78.1 (10.79)
MFV difference (cm/s)	8.8 (2.49)	9.7 (2.97)	14.4 (2.59)	19.9 (3.66)

Data are expressed as mean and standard deviation MFV, mean flow velocity; BHT, breath holding test

Table 3. Correlation between dMFV and clinical characteristics and laboratory parameters of participants.

Characteristics	Group-DRH d MFV (cm/s)		Group - DR d MFV (cm/s)		Group - H d MFV (cm/s)		Group - C d MFV (cm/s)	
	r	*P*	r	*P*	r	*P*	r	*P*
Age (years)	-0.42	.024	0.35	.060	-0.08	.672	0.00	.986
Duration of disease (H or DM) (years)	0.02	.935	-0.07	.715	-0.04	.843	NA	NA
BMI (kg/m^2)	-0.03	.883	0.08	.676	0.13	.488	0.11	.571
SBP (mmHg)	0.05	.778	0.10	.596	-0.25	.187	0.15	.435
DBP (mmHg)	0.12	.525	-0.14	.455	-0.26	.174	0.02	.933
HbA1c (%)	0.26	.161	-0.01	.950	-0.10	.588	0.09	.640
CRP (mmol/l)	0.04	.821	-0.22	.248	0.05	.814	0.09	.623

d MFV, difference of mean flow velocity; NA, not applicable

and the results are depicted in **Table 3**. There was significant correlation between cerebrovascular reactivity and age of participants in DRH group (r=-0.42; *P*=.024). None of the other correlations was significant.

DISCUSSION

To date, this is the first study which investigated cerebrovascular reactivity in hypertensive type 2 diabetics with retinopathy. In a previous studies, there have been reported contributions of diabetes mellitus and hypertension to impaired cerebrovascular reactivity, but it remains controversial different accompanying contribution of those pathological conditions attributable to cerebral vasodilatory response.[5,8,9] Analysing pathological changes of retinal blood vessels are helping to understand the causes of various cerebrovascular disorders. Retinopathy is related to incident clinical stroke and stroke mortality independent of blood pressure, diabetes, and other cerebrovascular risk factors. Retinal microvascular abnormalities seem to be markers of concomitant cerebral microangiopathy.[5,10] CVR is less intensive in patients with long-lasting type 2 diabetes mellitus and this impairment is inversely related to the duration of diabetes reported Fulesdi et al.[11] Ceravolo et al found that diabetic patients with proliferative retinopathy showed diminished vasodilatory responses as compared to those without retinopathy and with background retinopathy.[12] We performed our analysis on a group of subjects with a long disease duration more than 10 years based upon the observation that morphological changes of the microvessels develop approximately after 5-10 years disease duration. As type 2 diabetes mellitus is a more complex pathophysiological process, not only diabetes itself, but also hypertension and dyslipidemia should be taken into account. Thus, cerebral vasodilatory responses in type 2 diabetes could be also modified by accompanying hypertension. It has to be noted previously, that cerebral vasoreactivity tests using different stimuli (such as intravenous administration of acetazolamide, breath holding, and changes of the systemic blood pressure) all showed a decreased reactivity of the cerebral vessels in hypertensive patients.[13] We did not prove any difference in CVR in diabetics with retinopathy, with or without hypertension. Long-term diabetes is associated with endothelial dysfunction, with the predominance of vasoconstrictive factors and impaired endothelium-dependent vasorelaxation related to decreased nitric oxide synthesis. One of the major triggers of inadequate endothelium dependent vasodilation is the long-standing exposure to high lev-

els of glucose in the course of DM, which might affect basal tone and myogenic reactivity in the cerebral small vessels. Elevated glucose levels produce vasodilation and loss of intrinsic basal tone, thus rendering arteries incapable of responding adequately to various stimuli. Under these circumstances the impaired autoregulation of cerebral blood flow and the subsequent decreased vascular resistance in the downstream arterioles and capillaries may explain the reduced cerebrovascular reactivity in diabetics.[1] Kadoi depicted HbA1c as an indicator of the severity of diabetic microangiopathy in the brain.[5] In contrast, we did not find a significant correlation between the level of HbA1c and cerebral hemodynamic velocities. High BMI is associated with a reduction in cerebral blood flow velocities independent of diagnosis of type 2 diabetes mellitus and hypertension.[14] Our control participants without diabetes and hypertension are at lowest level of BMI with best response on BHT. Age is a factor associated with the CVR to hypercapnia.[5] Hartl et al reported that absolute and relative mean CO_2 reactivities in elderly subjects were markedly lower than those in young subjects.[15] Changes of CVR are not only related to aging, but they are influenced by hormonal changes.[16] In our data, age influences on CVR only in the group of diabetics with retinopathy and hypertension. Furthermore, impairment of CVR may be associated with increased markers of inflammation such as fibrinogen and CRP. These modifications are an argument for the structural and functional changes of cerebral small vessels. High plasma levels of CRP were associated with an increased risk of incident cardiovascular events among diabetic men, independent of currently established lifestyle risk factors, lipids, and glycemic control.[17] We did not notice a difference between groups according to the CRP value. The discrepancy between previous findings and our results in the correlation analysis may be related to the relatively small sample size. A considerable result of the present study is that type 2 diabetes mellitus affect CVR greater than sole hypertension because effective treatment of hypertension gradually normalizes the autoregulation of cerebral vessels and the results of vasoreactive tests do not differ from those of patients without hypertension.

REFERENCES

1. Petrica L, Petrica M, Vlad A: Cerebrovascular reactivity is impaired in patients with non-insulin-dependent diabetes mellitus and microangiopathy.Wien Klin Wochenschr 2007;119:365-371.
2. Fujii K, Sadoshima S, Okada Y, Yao H, Kuwabara Y, Ichiya Y, Fujishima M: Cerebral blood flow and metabolism in normotensive and hypertensive patients with transient neurologic deficits. Stroke 1990;21:283-290.
3. Settakis G, Pall D, Molnar C, Bereczki D, Csiba L, Fulesdi B: Cerebrovascular reactivity in hypertensive and healthy adolescents: TCD with vasodilatory challenge. J Neuroimaging 2003;13(2):106-12.
4. Inoue M, Azumi A, Yamamoto M: Ophthalmic artery blood flow velocity changes in diabetic patients as a manifestation of macroangiopathy. Acta Ophthalmol Scand 2000;78(2):173-6.
5. Kadoi Y, Hinohara H, Kunimoto F, Saito S, Ide M, Hiraoka H, Kawahara F, Goto F: Diabetic patients have an impaired cerebral vasodilatory response to hypercapnia under propofol anesthesia. Stroke 2003;34:2399-2403.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903.
7. Mankovsky BN, Ziegler D: Stroke in patients with diabetes mellitus.Diabetes Metab Res Rev 2004; 20:268-287.
8. Lucas SJE, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN: Influence of changes in blood pressure on cerebral perfusion and oxygenation. Hypertension 2010;55:698-705.
9. Ficzere A, Valikovics A, Fulesdi B, Juhasz A, Czuriga I, Csiba L: Cerebrovascular reactivity in hypertensive patients. A transcranial Doppler study. J Clin Ultrasound 1997;25:383-389.
10. Wong TY: Is retinal photography useful in the measurement of stroke risk? Lancet Neurol 2004;3(3):179-83.
11. Fulesdi B, Limburg M, Bereczki D, Kaplar M, Molnar C, Kappelmayer J, Neuwirth G, Csiba L: Cerebrovascular reactivity and reserve capacity in type II diabetes mellitus. J Diabetes Complications 1999;13:191-199.
12. Ceravolo MG, Lagalla G, Lippera S, Gregorio F, Provinciali L: Proliferative retinopathy predicts impairment in brain vasomotor reserve in type II diabetes. Cerebrovasc Dis 1997;7:332-338.
13. Pall D, Lengyel S, Komonyi E, Molnar C, Paragh G, Fulesdi B, Katona E: Impaired cerebral vasoreactivity in white coat hypertensive adolescents. Eur J Neurol 2011;18:584-589.
14. Selim M, Jones R, Novak P, Zhao P, Novak V: The effects of body mass index on cerebral blood flow velocity.Clin Auton Res 2008;18(6):331-338.
15. Hartl WH, Furst H: Application of transcranial Doppler sonography to evaluate cerebral hemodynamics in carotid artery disease. Stroke 1995;26:2293-2297.
16. Matteis M, Troisi E, Monaldo BC, Caltagirone C, Silvestrini M: Age and sex differences in cerebral hemodynamics. Stroke 1998;29:963-967.
17. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB: C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care 2004;27:889-894.