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Lack of gender difference in acetazolamide-induced cerebral vasomotor reactivity in patients suffering from type-1 diabetes mellitus

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Abstract The aim of the present work was to investigate the impact of gender on resting cerebral blood flow velocity and cerebrovascular reserve capacity among diabetic patients. Middle cerebral artery mean blood flow velocity (MCAV) was measured in 72 patients suffering from type 1 diabetes mellitus at rest and 5, 10, 15 and 20 min after intravenous administration of 1 g acetazolamide. Cerebrovascular reserve was calculated as the maximal percent increase in MCAV after acetazolamide. Resting MCAV and cerebrovascular reserve capacity were compared between males and females. Resting cerebral blood flow velocity was higher in diabetic females than in males (men, 55.0±17.0 cm/s; women, 64.4±12.6 cm/s, p=0.0094). Cerebrovascular reserve capacity was similar in diabetic women and men (men, 44.0%±18.6%; women, 52.6%±32.9%, p=0.17). Comparing MCAV and cerebrovascular reserve capacity among the diabetic subgroups with disease duration ≤10 years and >10 years, we did not detect any differences between women and men. Duration of diabetes was an important factor in determining cerebrovascular reserve capacity in both sexes: long-term diabetic women and men showed lower CRC values than diabetics with ≤10 years disease duration. Cerebrovascular reserve capacity is similar in diabetic women and men. Taking into consideration that cerebrovascular reserve is normally higher among women, our finding indicates a relatively more serious worsening of cerebral vasodilatory responses in women suffering from type 1 diabetes.

Key words Insulin-dependent diabetes mellitus • Cerebrovascular reserve capacity • Acetazolamide • Gender difference

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Introduction

Since Aaslid et al. [1] invented transcranial Doppler velocimetry, this method has been in continuous development. It enables noninvasive measurement of cerebral blood flow velocity both in resting state and after different stimuli. Previous observations reported reference values in control subjects [2] as well as in patients suffering from cerebrovascular diseases [3, 4]. In the recent decade transcranial Doppler measurements after vasodilatory stimuli have been performed in healthy volunteers [5–7] as well as in patients with diabetes [8, 9], hypertension [10], hypercholesterolemia [11], stenoses of the cerebral arteries [12], migraine [13], systemic lupus erythematodes [14], etc. Different stimuli – lowering or decreasing systemic blood pressure [15], CO_2 inhalation [16], cognitive tasks [17], breath holding [18], intravenous administration of acetazolamide [5, 12] – have been introduced to assess evoked blood flow velocity responses.

Numerous investigations have been published so far, however the clinical significance of testing cerebral vasodilatory responses is unclear. A possible explanation for

this uncertainty is the variety of factors which may influence cerebral blood flow velocity at rest and cerebral vasoreactivity. Age of the subjects, gender differences, hemorheologic factors, hemostatic variables, actual blood glucose, etc. were reported to play a modifying role and make interpretation difficult [8].

Previous investigations established that gender is a determining factor in resting cerebral blood flow velocity and in cerebrovascular reserve capacity (i.e. vasodilatory ability of the brain resistance arterioles). Female sex is associated with significantly higher resting blood flow velocity and cerebrovascular reserve in healthy controls compared with the opposite sex [5–7, 19, 20].

In recent studies, we detected impaired cerebrovascular reserve capacity in patients with insulin-dependent and non-insulin-dependent, diabetes mellitus [8, 9]. Vasodilatory ability was inversely related to duration of diabetes and it developed in parallel with other vascular complications of the disease. As diabetes has been reported to be a stronger vascular risk factor in diabetic women than in men [21–23], in the present study we investigated the impact of gender difference on resting cerebral blood flow velocity, cerebrovascular reactivity and cerebrovascular reserve capacity in diabetic patients.

Subjects and methods

Patients suffering from type 1 diabetes mellitus were studied. They were recruited from the Diabetes Outpatient Clinics of the County Hospital, Debrecen and the Academic Medical Centre, Amsterdam. All patients provided informed consent. Mean blood flow velocity of the middle cerebral artery (MCA) was measured using transcranial Doppler velocimetry, with the patients at rest and 5, 10, 15 and 20 min after intravenous administration of acetazolamide (Diamox, Lederle Parenterals, Puerto Rico, USA) as described earlier in detail [8, 9].

Cerebrovascular reactivity (CVR) was calculated as the percent increase of MCA mean blood flow velocity compared to the resting values:

$$CVR=\frac{(MCAV_{AZ}-MCAV_{rest})\times 100}{MCAV_{rest}}$$

where $MCAV_{AZ}$ is the mean blood flow velocity in the MCA after administration of acetazolamide (AZ), and $MCAV_{rest}$ is the resting mean blood flow velocity of the MCA.

The maximal percent increase in cerebral blood flow velocity after acetazolamide (cerebrovascular reserve capacity, CRC) was calculated as follows:

$$CRC=\frac{(MCAV_{AZMAX}-MCAV_{rest})\times 100}{MCAV_{rest}}$$

where $MCAV_{AZMAX}$ is the maximal mean blood flow velocity in the MCA after administration of AZ.

Patients were divided into two groups: females and males. In a further analysis subjects were grouped according to duration of diabetes: >10 years or ≤10 years.

Each patient underwent a routine laboratory investigation in the frame of regular screening of diabetes control: microalbuminuria, glycosylated hemoglobin, cholesterol and triglyceride concentrations were assessed. Although hemostatic parameters (fibrinogen, factor VIII antigen, alpha-2 macroglobulin) and serum insulin concentrations were also checked in a smaller cohort, the limited sample size of those patients did not allow the statistical analysis based on the previously mentioned grouping [8].

Statistical analysis

Values are reported as means and standard deviations. Parameters with normal distribution were compared using the appropriate *t* tests. Repeated measure analysis of variance was used to detect differences between the two gender groups in MCA mean blood flow velocity and cerebrovascular reactivity after acetazolamide. Analysis of variance was used to compare subgroups. When a significant difference was found among groups, the least significant difference (LSD) test was used for post hoc comparisons. Statistica for Windows v.5.1 (Statsoft, Tulsa, USA) software was used for statistical analysis.

The Local Ethical Committees of the University Medical School of Debrecen and of the Academic Medical Centre, Amsterdam, approved the study.

Results

We study 72 insulin-dependent diabetic patients (36 women and 36 men; mean age, 36.4±8.9 years; mean duration of diabetes, 15.5±9.7 years). There were 19 females and 15 males with diabetes mellitus for ≤10 years and 17 men and 21 women had a disease duration longer than 10 years. No differences in duration of diabetes were detected between women and men (females, 14.5±9.6 years; males, 15.1±9.4 years, p=0.8).

Glycosylated hemoglobin levels were similar in all groups, suggesting an appropriate control of diabetes (Table 1). Women with a disease duration more than 10 years had a higher urine microalbumin concentration as compared to any other groups. Serum cholesterol and triglyceride levels were comparable in the groups.

Resting cerebral blood flow velocity was significantly greater in women than in men (64.4±12.6 cm/s vs. 55.0±17.0 cm/s, p=0.0094) (Table 2). This gender difference did not reach statistical significance when patients with long-term disease were compared (Fig. 1, Table 2).

After the administration of acetazolamide, a significant gender effect (p≤0.004), was observed in the MCA blood flow velocity (data not shown). However, the time course of MCA mean blood flow velocity was similar in women and men. We detected a significant interaction between diabetes duration and time after acetazolamide (p≤0.0001).

Cerebrovascular reactivity, i.e. the percent increase in MCA blood flow velocity, was similar in both sexes.

Table 1 Laboratory parameters of the investigated subjects, by gender and disease duration. Means and standard deviations are shown

	Women		Men	
	<10 years	>10 years	<10 years	>10 years
Glycosylated hemoglobin (%)	8.8 (0.3)	9.4 (0.3)	8.8 (0.7)	9.5 (0.6)
Urine microalbumin (mg/day)	7.7 (1.2)	24.5 (8.5)	6.9 (1.0)	9.4 (1.5)
Cholesterol (mmol/l)	5.6 (0.2)	5.9 (0.3)	5.3 (0.3)	5.7 (0.3)
Triglyceride (mmol/l)	1.3 (0.3)	1.2 (0.1)	0.9 (0.1)	1.0 (0.1)

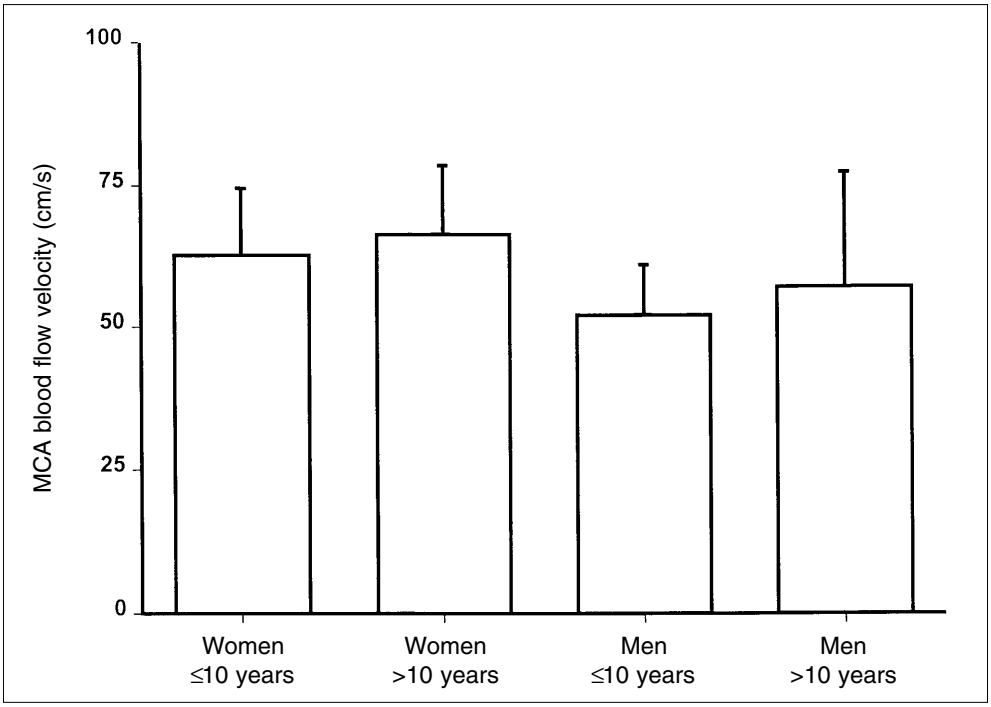

Fig. 1 Middle cerebral artery (MCA) mean blood flow velocity values (cm/s) in female and male patients suffering from diabetes for more than 10 years or for 10 years or less

Table 2 Results of least significant difference (LSD) test for comparing resting middle cerebral artery mean blood flow velocity values in the different subgroups. In the table *p* values are shown

	Women		Men	
	≤10 years	>10 years	≤10 years	>10 years
Women				
≤10 years	–	0.47	0.04	0.23
>10 years	0.47	–	0.009	0.06
Men				
≤10 years	0.04	0.009	–	0.33
>10 years	0.23	0.06	0.33	–

Additionally, the time course of cerebrovascular reactivity (i.e. the acetazolamide effect) was similar in women and men (p=0.31).

The cerebrovascular reserve capacity (CRC), i.e. maximal percent increase of MCAV after acetazolamide, was similar in diabetic men and women (44.0%±18.6% and 52.6%±32.9%, respectively, p=0.17). CRC of women with a disease duration ≤10 years was not significantly higher (p=0.06) than that of the corresponding group of men (Fig. 2, Table 3). In contrast, the CRC values of women and men were similar in the long-term diabetes groups (p=0.7).

Duration of diabetes was an important factor in determining cerebrovascular reserve capacity in both sexes: both long-term diabetic women and men had lower CRC values than diabetics with less than 10 years disease duration (Table 3).

Discussion

In a recent study, we demonstrated that cerebrovascular reserve capacity is impaired in patients with long-term type-1 diabetes mellitus [8]. In the present work we investigated whether this impairment is of similar magnitude in women and men. Although in general resting cerebral blood flow

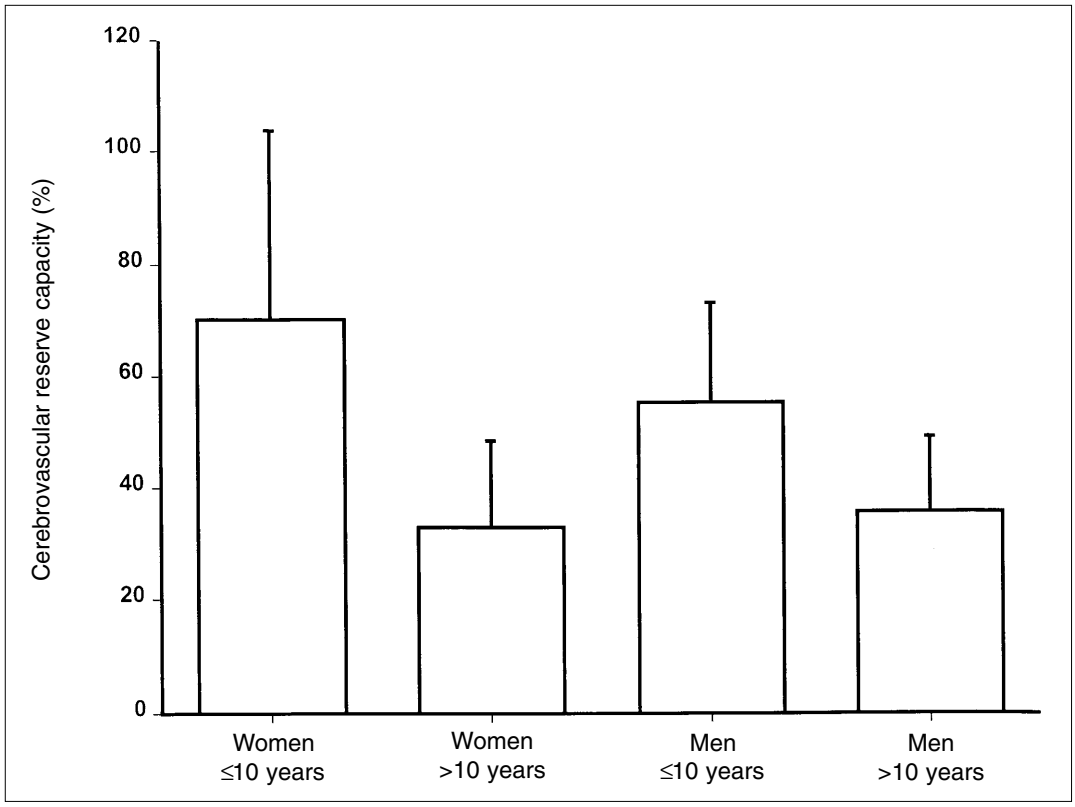

Fig. 2 Cerebrovacular reserve capacity values in female and male patients suffering from diabetes for more than 10 years or for 10 years or less

Table 3 Results of least significant difference (LSD) test comparing cerebrovascular reserve capacity values in the different subgroups. In the table p values are shown

	Women		Men	
	≤10 years	>10 years	≤10 years	>10 years
Women				
≤10 years	–	0.000005	0.060302	0.000008
>10 years	0.000005	–	0.006609	0.700781
Men				
≤10 years	0.060302	0.00669	–	0.012569
>10 years	0.000008	0.700781	0.012569	–

velocity was higher in diabetic women than in men, vasodilatory ability did not differ between the sexes. Although control subjects were not included in the present study, we have previously performed a series of acetazolamide vasoreactivity tests in healthy, non-diabetic patients [6]. We did not add those data to the present report on purpose, because we intended to compare cerebral vasoreactivity among diabetic female and male individuals, in order to clarify the role of gender in determining cerebral vasoreactivity.

Similar to our diabetic patients, resting cerebral blood flow velocity has been found to be higher in healthy women as compared to men [6, 7, 19, 20]. The exact explanation for this finding is unclear. Lower hematocrit and thinner arteries of women, and the influence of female sex hormones have been implicated [6].

Cerebral vasoreactivity has also been demonstrated to be higher in females than in males. Brouwers et al. [20] found that this difference is not present in childhood, but appears in adolescence and thereafter is present until the age of over 60 years. Using acetazolamide as vasodilatory stimulus, Karnik et al. [5], Oláh et al. [6] and Valikovics et al. [7] demonstrated also higher vasoreactivity among adult women. Similar to resting cerebral blood flow, the explanation for higher cerebral vasoreactivity of healthy female individuals is also unknown. In our previous report we speculated that smooth muscle of females is more sensitive to the vasodilatory stimulus than that of males [6]. This theory is supported by the observation of Brouwers et al. [20] who demonstrated that cerebral vasoreactivity is higher in women over wide ranges of pCO_2. On the other hand, it is obvious that these differences can be observed only after a certain age. As higher vasoreactivity in female individuals appears in adolescence and disappears in the elderly [6], this underlines the possible role of female sex hormones in determining cerebral vasodilatory responses.

It is widely accepted that diabetes mellitus affects cerebral vasculature [21, 24–27]. Both macro- and microangiopathy may occur. Previous studies demonstrated that diabetes is a stronger risk factor for cardiovascular diseases in females than in males [21–23, 28]. A possible explanation for this finding is the observation of Pyörala et al. [26] who demonstrated that diabetes reduces the female protective factor for premature atherosclerosis. We have shown that gender differences in cerebral vasoreactivity (i.e. the vasodilatory ability of the cerebral arterioles) observed in healthy subjects disappear already in early phase of diabetes mellitus. As vasoreactivity normally is higher in female individuals than in males, it is conceivable that the relative worsening of cerebral vasodilatory responses is more serious in women. Although the clinical significance and predictive power of impaired cerebrovascular reserve capacity is still unknown, it may be a logical explanation for the gender differences observed in the incidence of strokes among diabetic subjects.

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