Young Patients With Diabetes Have Decreased Cerebrovascular Reactivity Under Hypercapneic Conditions

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ABSTRACT

OBJECTIVE: Adult diabetic patients have an abnormal cerebrovascular response to hypercapnia, but there are few studies focused on diabetes mellitus type 1 and cerebral blood flow in pediatric or adolescent patients. We hypothesize that young patients with diabetes exhibit a different response to hypercapnia than normal control counterparts. METHODS: Using transcranial Doppler techniques, we compared young diabetic patients with healthy controls by measuring cerebral blood velocity before and during carbon dioxide challenge. RESULTS: Subjects with diabetes had decreased cerebral blood velocity reactivity when compared with the control group (P = 0.005). CONCLUSION: Our results suggest cerebrovascular dysfunction in diabetic patients beginning at an early age. The possibility of long-term implications for cerebrovascular disease demonstrates the need for further studies in the pediatric and adolescent diabetic population to better understand this prevalent condition.

Keywords: transcranial Doppler, cerebral blood flow, hypercapnia, adolescents and youth

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Background

Measurement of cerebral blood flow or velocity under hypercapneic conditions has been used as a marker of cerebrovascular reactivity, which may indicate level of endothelial function.1 Using a transcranial Doppler, we previously studied cerebral blood velocity in hypertensive adolescents during carbon dioxide (CO2) challenge. Results showed that hypertensive adolescents had reduced cerebrovascular reactivity compared with age-adjusted normotensive controls.2 Hypertensive children with low cerebrovascular reactivity have been found to exhibit decreased executive function as measured through the Behavior Rating Inventory of Executive Functions test.3 We concluded that hypertension impairs cerebrovascular reactivity, suggesting endothelial dysfunction in as early as adolescence.

In this study, we employed similar techniques to assess whether young patients with diabetes mellitus type 1 also had impaired cerebrovascular reactivity. A review of literature pertaining to diabetes mellitus type 1 and cerebral blood flow revealed few studies in pediatric or adolescent subjects.

Two studies of diabetic subjects assessed cerebral blood flow with and without hypercapnia using xenon techniques.4,5 Few of the diabetic patients studied were younger than 21 years; Dandona et al.4 reported a range of age 14 to 74 years without listing individual ages, and Griffith et al.5 included one 18-year-old and one 19-year-old diabetic subject of 22 participants. Both studies found abnormal CO2-induced reactivity in the diabetic group compared with the control group.

Four studies evaluated cerebrovascular reactivity in adult diabetic patients using techniques other than CO2 challenge. Bentsen et al.6 studied cerebral blood flow with
xenon and found that patients with diabetes had lower reactivity to blood pressure manipulations. Another study used transcranial Doppler and found that adults with proliferative diabetic retinopathy also had an abnormal cerebrovascular response to blood pressure manipulation. Another study used transcranial Doppler and acetazolamide to show impairment of cerebrovascular reactivity in adults with long-term diabetes mellitus type 1. The final study showed that hypoglycemia-induced increases of cerebral blood flow were blunted in patients with diabetes.

As for studies in children, Hoffman et al. measured cerebral blood flow velocity using transcranial Doppler in 17 diabetic male subjects between ages 12 and 20 years. When compared with healthy control subjects, these patients did not exhibit significant differences in cerebral blood flow during CO2 challenge. Furthermore, duration of diabetes, insulin dose, or degree of glycemic control did not influence the reactivity of cerebral vasculature. Another pediatric study looked at cerebral circulation in diabetic children but focused only on the ketoacidotic state.

The literature suggests that adult diabetic patients have an abnormal cerebrovascular response to hypercapnia. There is only one pediatric study showing no effect of hypercapnic reactivity in diabetic children compared with controls, but the study did not compare reactivity over multiple measurements. We hypothesize that young patients with diabetes exhibit a different response to hypercapnia than normal control counterparts. Here, we present our findings on cerebrovascular reactivity in a group consisting of nine adolescents and one young adult, all with diabetes mellitus type 1. Our aim is to provide further insight on the process affecting cerebral vasculature in young patients with this prevalent disease.

Methods

Study protocol

Seven male and three female patients (mean age 16.3 years, range 12-24 years) (n = 10) under insulin treatment for type 1 diabetes mellitus were recruited for our study through referral by the pediatric endocrinology clinic. Length of time from date of diabetes diagnosis ranged from 7 months to 16 years. Aside from one case of asthma and heart murmur, all participants were free of any other chronic illness. None of the participants required medication the day of data collection other than the prescribed insulin. A control group (n = 13) of nondiabetic, well adolescents was also assembled for comparison (nine males and four females, mean age 15.2, range 11-19 years). Both groups were normotensive by history and on examination at entry. None of the adolescents recruited had clinical autonomic dysfunction or signs or symptoms of neuropathy.

Each subject was asked to come for a single session of transcranial Doppler data collection. In a comfortable sitting position and with a nose clip in place, participants breathed and rebreathed through a mouthpiece connected to a sealed bag. A capnometer (BCI Capnocheck-Capnograph; DRE, Louisville, KY) connected to the mouthpiece measured end-tidal CO2, while a transcranial Doppler (Smart-Lite transcranial Doppler, Rimed Ltd, Raanana, Israel) simultaneously measured velocity in the middle cerebral artery through the temporal window. Time-averaged maximum mean (TAMM) velocity and time-averaged mean (TAM) velocity measurements were recorded every 10 seconds and stopped when CO2 reached a plateau or when the participant could no longer tolerate the procedure. After a rest period of at least 5 minutes, participants were asked to repeat the protocol if they were able to tolerate a second run.

Data analysis

Variables were described in terms of mean ± standard deviation for normally distributed variables (e.g., age) and in terms of frequency (percentage) for categorical variables (e.g., gender). Differences in the degree of relationship between CO2 and TAMM velocity were analyzed using mixed model regression, which allowed us to look at CO2 and TAMM velocity as repeated measures while simultaneously taking into account variability within each subject. The interaction between CO2 and group membership (diabetic versus control) was used to test for differences in the regression slope between the groups. This term tested for whether the slope between CO2 and TAMM velocity was dependent on group (diabetic versus control). A similar analysis was done between CO2 and TAM velocity as a check. A Box-Cox transformation was used to correct for skewness in the case of CO2. The statistical program SAS 9.3 (SAS Inc, Cary, NC) was used for all analyses, and a level of significance <0.05 was used for all statistical tests.

Results

Characteristics of the two groups of subjects were similar (Table). Mean age was 16 years for the diabetic group and 15 years for the control group. About 70% of the subjects in each group were males. Subjects in the diabetic group were more likely to have only one run of the CO2 challenge (60% in the diabetic subjects versus 23% in the control subjects; P = 0.10). Body mass index data were available for all diabetic subjects and five of 13 subjects in the control group. There were no significant baseline differences between the groups in terms of body mass index (P = 0.50), systolic blood pressure (P = 0.31), diastolic blood pressure (P = 0.16), CO2 (P = 0.91), TAMM velocity (0.78), or TAM velocity (P = 0.29).

TAMM velocity was regressed onto CO2, and regression lines were drawn separately for the diabetic group and the control group (Fig 1). The linear regression line for the diabetic group had a lower slope (B = 1.08) than the regression line for control subjects (B = 1.34). Based on the mixed model regression and controlling for differences in the number of runs between the groups, the interaction term testing for differences in slope between diabetic and controls subjects was significant (P = 0.005), which confirmed the lower slope observed in the diabetic group. Even after controlling for age and gender in the model, the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetic Subjects (n = 10)</th>
<th>Control Subjects (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.3 ± 3.7</td>
<td>15.2 ± 2.4</td>
<td>0.41</td>
</tr>
<tr>
<td>Male gender</td>
<td>7 (70%)</td>
<td>9 (69%)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI</td>
<td>22.6 ± 3.8</td>
<td>24.3 ± 6.1*</td>
<td>0.50</td>
</tr>
<tr>
<td>One run only</td>
<td>6 (60%)</td>
<td>3 (23%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>105.3 ± 6.8</td>
<td>108.5 ± 7.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>67.4 ± 10.5</td>
<td>72.7 ± 6.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline CO2 (mm Hg)</td>
<td>33.6 ± 5.0</td>
<td>32.2 ± 8.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Baseline TAMM velocity (cm/s)</td>
<td>91.4 ± 15.2</td>
<td>94.0 ± 25.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Baseline TAM velocity (cm/s)</td>
<td>61.4 ± 9.4</td>
<td>69.2 ± 20.9</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Abbreviations:
- BMI = Body mass index
- DBP = Diastolic blood pressure
- SBP = Systolic blood pressure
- TAM = Time-averaged mean
- TAMM = Time-averaged maximum mean

* Value reflects data from n = 5.
group × CO₂ interaction remained significant (P = 0.004). Looking only at the data for the first run, we found a similar and significant group × CO₂ interaction (P = 0.02).

The individual trend lines for the subjects in each group were consistent with the overall difference indicated by the significant interaction (Figs 2 and 3). In general, the slopes of the individual lines for the diabetic subjects were lower than the slopes for the control. TAMM velocity was highly correlated with TAM velocity (r = 0.97, P < 0.001), and analyzing the group × CO₂ interaction for TAM velocity also showed a significantly lower regression slope for the diabetic group (P = 0.01). In addition, gender was a significant covariate of TAMM velocity with female subjects in general showing a higher TAMM velocity (P = 0.046). Girls also showed a quicker rise than boys in response to CO₂ (P = 0.002).

**Discussion**

The diabetic subjects had lower slope than the control group, suggesting that patients with type 1 diabetes mellitus have decreased cerebrovascular reactivity, which has not been previously reported in a study of young patients. As mentioned earlier, Hoffman et al.¹⁰ did not find a significant difference in cerebral blood flow between diabetic and control adolescents. The discrepancy in our results may be explained by differing data analyses. The previous study examined differences between the groups by comparing the percent change between pretest and posttest transcranial Doppler measurements. In contrast, we performed a regression of all data points, creating a separate slope for the diabetic subject group and the control group. We then compared the two slopes, thus allowing for inclusion of the velocity-to-CO₂ relationship differences observed to occur across the physiologic CO₂ range. It is worthwhile to mention that changes in blood pressure during each run as a response to increase of CO₂ could impact blood flow velocity.¹² However, both groups were treated similarly and a regression was obtained for each group. Therefore, any consequence of blood pressure on cerebral blood flow velocity was included in the data analysis, and this would not change our overall conclusions.

Our data analysis found that female subjects had a significantly higher TAMM velocity than male subjects. This result is consistent with previous research in healthy patients showing that girls have higher flow velocities in the middle cerebral artery than boys.¹³ It may also be related to our finding that girls had a quicker rise in response to CO₂. The reason for this is unclear but may have to do with innate blood pressure differences between genders.¹⁴
Limitations of our study include a small sample size. Although we reported gender differences in TAMM velocity, this finding is based on a sample size of only three female diabetic subjects and should be interpreted with caution. Furthermore, the small sample does not allow for clinical subtyping. The diabetic subjects were all under treatment with insulin, but they had varying degrees of disease control. Three diabetic subjects had much lower slopes than the majority, but conclusions cannot be made as to what characteristics of these particular subjects contributed to the lower results. We did not attempt to calculate slopes on individual patients. A larger sample size is needed to offer a more comprehensive representation of the range of glycemic control within the adolescent diabetic population.

Clinically, transcranial Doppler techniques have been useful in the setting of cerebrovascular disorders such as subarachnoid hemorrhage, cerebral vasospasm, intracranial steno-occlusive disease, acute ischemic stroke, collateral flow, sickle cell disease, microemboli detection, and cerebral circulatory arrest. We also saw that decreased cerebrovascular reactivity may be a reflection of endothelial dysfunction in hypertensive adolescents and possible cognitive consequences. Because of the noninvasive and painless nature of this study, transcranial Doppler with CO₂ challenge may be an option to monitor vascular disease progression in young patients with diabetes. In subjects who are cooperative with the protocol, TAMM velocity slope may predict vascular disease.

Additional studies are required to better understand how diabetes sequelae impede cerebral blood flow. Future research should study factors for cerebrovascular abnormalities in the diabetes mellitus type 1 patient population, including measures of diabetes control, obesity, hyperlipidemia, hypertension, and autonomic neuropathy. Obese children with diabetes mellitus type 1, although none of our patients were obese, have a higher prevalence of hypertension and dyslipidemia than their counterparts of healthy weight. Poor diabetes control in adolescents has been shown to be a risk factor for abnormal mean systolic blood pressure and therefore may impact cerebrovascular reactivity. Although a baseline measurement was taken at the start of the transcranial Doppler, continuous blood pressure evaluation for 24 hours and throughout the study would give a more meaningful picture of blood pressure status. Presence of autonomic neuropathy in chronic diabetic patients could also impact blood pressure. A study of 45 male diabetic patients found that cerebrovascular response to CO₂ was reduced in those with autonomic neuropathy compared with nondiabetic controls. Based on adult type 2 diabetes data, comorbid factors influencing cerebrovascular reserve were not found. It is not clear whether these findings are also applicable to young patients with type 1 diabetes. Accordingly, there is a need to elucidate which pediatric diabetic patients are at risk for abnormal CO₂ transcranial Doppler measurements and how these abnormalities predict future cerebrovascular disease and potentially cognitive function.

Conclusion

Compared with healthy control subjects, young patients with diabetes had decreased cerebrovascular reactivity in response to hypercapnia. This finding has not been previously reported in this population and suggests cerebrovascular dysfunction in diabetic patients beginning at an early age. The possibility of long-term implications for cerebrovascular disease demonstrates the need for further studies in pediatric and adolescent patients with diabetes mellitus type 1 to better understand this prevalent condition.

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References


