Impact of Fasting Glycemia and Regional Cerebral Perfusion in Diabetic Subjects
A Study With Technetium-99m-Ethyl Cysteinate Dimer Single Photon Emission Computed Tomography

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Background and Purpose—Diabetes mellitus increases the risk of ischemic stroke. The aim of this study was to investigate the correlation between fasting plasma glucose (FPG) and changes in regional cerebral perfusion (CP) in subjects with DM.

Methods—CP was assessed in 24 subjects (mean age 44±2.5 years) with type 1 diabetes mellitus by single photon emission computed tomography.

Results—Analysis of CP during elevated FPG (224±24 mg/dL) showed 3 or more deficits in 42% of the subjects. A positive relationship between the number of CP deficits and FPG was observed (P<0.01), but not with age, sex, body mass index, or duration of diabetes mellitus. Regional deficits were reduced (P<0.001) with improvement in FPG (119±5 mg/dL). This reduction remained significant after adjustment for age, sex, and body mass index. Plasma levels of P-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, established markers of endothelial dysfunction, were significantly decreased with lower FPG. Furthermore, thiobarbituric acid reactive substance plasma levels, an index of oxidative stress, were also reduced (P<0.01).

Conclusions—The present study demonstrates that changes in FPG are associated with functional changes in regional CP. Hyperglycemia-induced endothelial dysfunction may be implicated in the impaired regional CP of diabetic subjects. (Stroke. 2009;40:306-308.)

Key Words: cerebral blood flow ■ diabetes mellitus ■ endothelium ■ SPECT

Diabetes mellitus is a well-recognized risk factor for ischemic stroke. It is estimated that the risk of stroke is increased by 1.5- to 3-fold for patients with diabetes.1,2 Diabetes also doubles the risk of stroke recurrence and outcomes are significantly worse.3 In the UK Prospective Diabetes Study (UKPDS) trial, the OR for case fatality in stroke was 1.37 per 1% HbA1c increase.4 Hyperglycemia-induced endothelial dysfunction may contribute to the association between poor glycemic control and adverse cerebrovascular outcomes.5 Previous studies6,7 performed in poorly controlled patients with diabetes by single photon emission computed tomography (SPECT) have shown reduced regional cerebral blood flow (rCBF) before the onset of stroke. In none of these studies, however, was the modulation of cerebral perfusion (CP) exerted by plasma glucose levels investigated and the potential pathophysiological mechanisms involved are unclear.

The present study was designed to characterize the link among fasting plasma glucose (FPG), changes in CP assessed by SPECT, and markers of hyperglycemia-induced endothelial dysfunction.

Methods
Protocol
We studied 24 subjects with type 1 diabetes mellitus (18 males and 6 females; mean age, 44±2.5 years) free of detectable cardiovascular complications. The known average duration of diabetes was 7.5±1.5 years. rCBF was assessed by SPECT. Plasma levels of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, P-selectin, and thiobarbituric acid reactive substance were also measured. SPECT imaging and biochemical determinations were repeated after a good glycemic control was achieved by dietary recommendations and subcutaneous insulin administration (HbA1c <7%; average time interval between the 2 perfusion studies: 3 to 7 months). All subjects were studied after...
As shown in Figure 1A, the higher the FPG, the greater the frontal regions were most frequently affected by CP deficits. 42% of the subjects with high FPG. Temporal and posterior–frontal–mid regions of interest were selected in each hemisphere to evaluate cerebral technetium-99m-ethyl cysteinate dimer uptake (see Figure 1). The cerebellar region of interest was considered as reference region with maximal uptake. A semiquantitative analysis (perfusion index [R]=[Ix100]/C; I=region of interest; C=cerebellar activity) was performed by blinded investigators. Deficit of perfusion was defined if the perfusion index was <10% of that measured in the reference region.

Figure 1. A, Correlation of FPG and CP deficits. Results are mean±SEM. B, Representative CBF changes assessed by technetium-99m-ethyl cysteinate dimer SPECT at baseline and after reduction in FPG according to colorimetric scale. The regions of interest are anterior (1), mid (2), posterior–frontal (3), parietal (4), temporal-parietal (5), tempo-occipital (6), perisylvian (7), temporal (8), and cerebellar (9), respectively.

Laboratory Measurements
Plasma glucose was measured by the glucose oxidase method. Serum cholesterol and triglycerides were measured by standard enzymatic methods (Roche Diagnostic); and vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and P-selectin by enzyme-linked immunoassay (DIACLONE Research, Besancon, France). Plasma levels of lipid peroxidation were determined with thiobarbituric acid reactive substance assay kit (OxiTeck, ZeptoMetrix, New York, NY).

Statistical Analysis
Data are presented as mean±SD unless otherwise stated. Differences in measured variables between baseline and reduced FPG were compared using Student t test. Analysis of variance was performed to explore the difference in FPG among subjects with different CP deficits. Analysis of covariance was used to adjust for selected variables. Univariate linear regression analysis was carried out by Pearson’s correlation. Statistical significance was inferred at P<0.05.

Table. Patient Characteristics

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Low FPG</th>
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<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>26±1</td>
<td>25±1</td>
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<tr>
<td>FPG, mg/dL</td>
<td>224±24</td>
<td>119±5*</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124±16</td>
<td>118±10</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80±8</td>
<td>78±8</td>
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<tr>
<td>Cholesterol, mg/dL</td>
<td>194±36</td>
<td>199±32</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>120±56</td>
<td>117±67</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.87±0.1</td>
<td>0.86±0.1</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 versus baseline.
glycemic control, functional changes of regional CP, and markers of hyperglycemia-induced endothelial dysfunction. Several lines of evidence support our conclusion. A significant correlation was demonstrated between number of CP deficits and FPG. Indeed, the deficits observed in the study patients at baseline were significantly reduced with improvement in FPG. Furthermore, our semiquantitative analysis of rCBF by SPECT showed glycemia-dependent CP deficits in temporal and posterior–frontal regions of interest, which are the most common regions susceptible to cerebrovascular accidents. Interestingly enough, the amelioration of rCBF was associated with decreased plasma levels of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, P-selectin as well as thiobarbituric acid reactive substance. Our data do not allow a definite conclusion about pathophysiological pathways linking good glycemic control to improved CP. However, based on our previous experimental observations, we hypothesize that hyperglycemia may cause endothelial dysfunction by eliciting reactive oxygen species-mediated inactivation of nitric oxide, and subsequent reduced nitric oxide bioavailability results in an increase of transcription factor NF-kB activity and upregulation of adhesion molecules expression. Pro-oxidative and proinflammatory changes leading to hyperadhesiveness of endothelium in response to hyperglycemia may affect rCBF in patients with insulin-dependent diabetes. Hence, hyperglycemia-induced endothelial dysfunction may play an important role in the pathogenesis of rCBF abnormalities, which will ultimately result in a high incidence of cerebrovascular events.

Disclosures

None.
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