Altered Prefrontal Glutamate–Glutamine–γ-Aminobutyric Acid Levels and Relation to Low Cognitive Performance and Depressive Symptoms in Type 1 Diabetes Mellitus

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Context: Neural substrates for low cognitive performance and depression, common long-term central nervous system–related changes in patients with type 1 diabetes mellitus, have not yet been studied.

Objective: To investigate whether prefrontal glutamate levels are higher in patients with type 1 diabetes and whether an elevation is related to lower cognitive performance and depression.

Design: Cross-sectional study.

Setting: General clinical research center.

Participants: One hundred twenty-three patients with adult type 1 diabetes with varying degrees of lifetime glycemic control and 38 healthy participants.

Main Outcome Measures: With the use of proton magnetic resonance spectroscopy, prefrontal glutamate–glutamine–γ-aminobutyric acid (Glx) levels were compared between patients and control subjects. Relationships between prefrontal Glx levels and cognitive function and between Glx levels and mild depressive symptoms were assessed in patients with type 1 diabetes.

Results: Prefrontal Glx concentrations were 9.0% (0.742 mmol/L; \( P = .005 \)) higher in adult patients with type 1 diabetes than in healthy control subjects. There were positive linear trends for the effects of lifetime glycemic control on prefrontal Glx levels (\( P \) for trend = .002). Cognitive performances in memory, executive function, and psychomotor speed were lower in patients (\( P = .003, .01, \) and < .001, respectively) than in control subjects. Higher prefrontal Glx concentrations in patients were associated with lower performance in assessment of global cognitive function (0.11 change in \( z \) score per 1-mmol/L increase in Glx) as well as with mild depression.

Conclusions: The high prefrontal glutamate levels documented in this study may play an important role in the genesis of the low cognitive performance and mild depression frequently observed in patients with type 1 diabetes. Therapeutic options that alter glutamatergic neurotransmission may be of benefit in treating central nervous system–related changes in patients with adult type 1 diabetes.
without a clamp design, showed elevated cerebral glucose levels.\(^{11,13-15}\)

Given that cerebral glucose catabolism and the tricarboxylic acid cycle are closely coupled to the glutamine-glutamate cycle,\(^{16,17}\) high cerebral glucose levels in patients with T1DM might be expected to lead to increased glutamate synthesis. Furthermore, antibodies to the glutamate decarboxylase (GAD) enzyme, which may also alter cerebral glutamate levels, have been found in the majority of patients with T1DM tested even during the early phase of disease.\(^{18-20}\) Although glutamate, a major excitatory neurotransmitter, and its receptors have key roles in processes of learning and memory,\(^{21}\) overstimulation potentially damages neuronal cells owing to calcium overload.\(^{22}\) Maintaining the optimal balance of this major neurotransmitter in the CNS may thus be critically important.\(^{23}\)

However, to our knowledge, the possibility of a sequential cascade starting from an increased cerebral glucose level, resulting in disturbed cerebral glutamate homeostasis and the eventual lowering of cognitive performance and depression, has not yet been studied in patients with diabetes. In an era when measurement of cerebral glucose and glutamate levels is increasingly available,\(^{16,17}\) this knowledge in the target organ might provide more direct information for controlling CNS-related changes in diabetes, including suggestions for better treatment options.

We conducted proton MRS imaging to measure prefrontal glutamate–glutamine–γ-aminobutyric acid (Glx) and glucose levels and assessed cognitive function and current depressive symptoms in a large cohort of adult patients with T1DM with varying degrees of lifetime glycemic control and in healthy control subjects. This study provided a unique opportunity to examine the association between prefrontal metabolite levels and cognitive function in a naturalistic and clinical environment.

We hypothesized that prefrontal Glx levels would be higher in adult patients with T1DM than in healthy control subjects and that higher prefrontal Glx levels would be associated with lower cognitive function and depression in patients with T1DM. We also aimed to determine whether the relationship between prefrontal Glx levels and cognitive function in adult patients with T1DM would differ from that in healthy control subjects, thus indicating differential effects of prefrontal Glx on cognitive function in normal and pathological conditions.

Considering the beneficial effects of stringent glycemic control on cognitive function,\(^{8,24}\) we additionally examined whether maintaining the glycemic control within target (lifetime glycated hemoglobin [HbA\(_1c\)] level <7%) rather than beyond target (≥7%) would be beneficial in keeping cerebral glucose and glutamate homeostasis within the normal range. (To convert HbA\(_1c\) level to a proportion of total hemoglobin, multiply by 0.01.)

### METHODS

#### PARTICIPANTS

Study participants consisted of 123 adult patients with T1DM and 38 healthy control subjects. Patients with T1DM who consecutively visited the Joslin Diabetes Center, Boston, Massa-
medical records or patient self-report. Hand preference was evaluated by the Edinburgh Handedness Inventory.34

Current HbA1c levels, measured approximately 30 minutes before the start of MR imaging, were used as a measure of recent ambient blood glucose levels in the present study. Detailed methods and results for the acquisition of data pertaining to the relationship between recent peripheral glycemia and prefrontal glucose levels are described in eSupplement 1 (http://www.archgenpsychiatry.com).

MR IMAGE ACQUISITION AND PROTON MRS

The MR imaging was conducted at the McLean Brain Imaging Center with the use of a 1.5-T whole-body imaging system (Horizon LX; GE Medical Systems, Milwaukee, Wisconsin). All images were obtained with the use of a custom-made linear birdcage coil with approximately 40% improvement in the signal to noise ratio and improved homogeneity over a standard quadrature head coil.35 A 3-dimensional spoiled gradient echo pulse sequence was used to produce 124 contiguous coronal images, 1.5 mm thick (echo time [TE], 5 milliseconds; repetition time [TR], 35 milliseconds; matrix, 256×192; field of view [FOV], 20 cm; flip angle [FA], 45°; and number of excitations [NEX], 1). Axial T2-weighted images (TE, 80 milliseconds; TR, 35 milliseconds; matrix, 256×192; flip angle, 90°; and NEX, 1) were also included into the LCModel fitting to control for their contribution.39,40 Short-echo localized proton MRS has been used in detecting high cerebral glucose resonances, which are reflected by peaks at 3.43 ppm, in patients with T1DM.13,15

The relative MRS metabolite levels were expressed as the ratio of each metabolite peak to the Cr peak at 3.0 ppm. Spectral quality and reliability of fit for all metabolites were adequate, and the detailed descriptions are presented in eSupplement 2. The mode, median, and mean values of relative error estimates (Cramer-Rao lower bound values) for each metabolite, calculated by the LCModel, are presented in eTable 1. To control for the effects of tissue composition on prefrontal metabolite levels, gray matter (GM), white matter, and cerebrospinal fluid volumes in the VOI were measured. There were no differences in the proportions of GM, white matter, or cerebrospinal fluid volumes in the VOI.41 Furthermore, to control for variations of metabolite concentrations between GM and white matter, final analyses were conducted with the GM proportion of each VOI used as a covariate.
Validation for quantifying metabolites in the phantom was conducted as a measure of the reproducibility (eTable 3). Coefficients of variation for each metabolite suggest that LCModel-fitted metabolite concentrations from the phantom were highly reproducible over the study period.

Figure 2 shows the sample spectra, which were measured in a patient with T1DM and a corresponding healthy control subject.

STATISTICAL ANALYSIS

Independent t test/analysis of variance and χ² test were used for comparing continuous and categorical variables, respectively. Prefrontal metabolite concentrations were compared between adult T1DM and healthy control groups by means of an analysis of covariance with age, sex composition, and GM proportion as covariates.

To evaluate how the level of long-term glycemic control is associated with prefrontal metabolite concentrations, values were compared between T1DM subgroups, as divided by degree of lifetime glycemic control (good vs poor) relative to control subjects, using the analysis of covariance with a test for linear trend.

There was no significant difference in age, sex composition, educational level, handedness, or proportion of smokers between adult T1DM and healthy control groups or between the 2 T1DM subgroups (Table 1). However, the healthy control group included more nonwhites than did the adult T1DM group (P < .001). The 2 T1DM subgroups did not differ in most diabetes-specific clinical characteristics of duration of illness, age at onset, or the number of hypoglycemic episodes, but there was a difference in the lipid profile (Table 1).

Prefrontal metabolite concentrations and ratios to Cr are shown in Table 2. Prefrontal glucose concentrations were higher, by 88.9% (0.872 mmol/L), in adult patients with T1DM than in healthy control subjects (F₁,₁₄₂ = 26.10, P < .001). There was a positive linear trend (a dose-responsive pattern, healthy control group vs good vs poor glycemic control T1DM subgroups) for the relationship between lifetime glycemic control and prefrontal glucose concentrations (P for trend < .001; Figure 3).

Prefrontal Glx concentrations were 9.0% higher (0.742 mmol/L) in adult patients with T1DM than in healthy control subjects (F₁,₁₃₁ = 8.15, P = .005). A linear trend for the relationship between lifetime glycemic control and prefrontal Glx concentrations was observed (P for trend = .002; Figure 3). This linear trend remained unchanged when the smoking status was included as an additional covariate (P values of the Glx difference between groups = .01; P for trend = .004).
Patients with type 1 diabetes were divided into good (within the treatment target range) and poor glycemic control subgroups according to the level of lifetime average glycated hemoglobin. Patients with good glycemic control were defined as those with a lifetime average glycated hemoglobin level less than 7%. Patients with type 1 diabetes.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

**Table 1. Demographic and Clinical Characteristics of 123 Patients With Type 1 Diabetes Mellitus and 38 Healthy Control Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects (n = 38)</th>
<th>All Diabetic Patients (n = 123)</th>
<th>P Value, Control Subjects vs All Patients</th>
<th>Type 1 Diabetic Patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value, Good vs Poor Glycemic Control Subgroups&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>30.8 (5.1)</td>
<td>32.3 (4.4)</td>
<td>.09</td>
<td>32.9 (4.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Sex, No. (%) F</td>
<td>18 (47)</td>
<td>51 (58)</td>
<td>.26</td>
<td>11 (50)</td>
<td>.60</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>17.4 (1.9)</td>
<td>16.4 (3.2)</td>
<td>.06</td>
<td>17.0 (2.2)</td>
<td>.31</td>
</tr>
<tr>
<td>Right-handed, No. (%)</td>
<td>35 (92)</td>
<td>119 (97)</td>
<td>.22</td>
<td>21 (95)</td>
<td>.98</td>
</tr>
<tr>
<td>Current smoker&lt;sup&gt;b&lt;/sup&gt;, No. (%)</td>
<td>1 (3)</td>
<td>5 (4)</td>
<td>.60</td>
<td>0</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (76)</td>
<td>116 (94)</td>
<td>.001</td>
<td>20 (91)</td>
<td>.96</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>9 (24)</td>
<td>7 (6)</td>
<td>.001</td>
<td>96 (95)</td>
<td>.37</td>
</tr>
<tr>
<td>Medical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>51.4 (14.7)</td>
<td>57.5 (16.2)</td>
<td>.04</td>
<td>56.0 (14.3)</td>
<td>.57</td>
</tr>
<tr>
<td>LDL-C</td>
<td>106.6 (32.8)</td>
<td>112.0 (34.0)</td>
<td>.39</td>
<td>106.9 (20.1)</td>
<td>.111</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>179.2 (32.4)</td>
<td>185.3 (40.9)</td>
<td>.39</td>
<td>174.9 (24.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>101.8 (36.6)</td>
<td>84.1 (62.8)</td>
<td>.12</td>
<td>58.4 (28.3)</td>
<td>.04</td>
</tr>
<tr>
<td>Blood glucose&lt;sup&gt;c&lt;/sup&gt;, mean (SD), mg/dL</td>
<td>NA</td>
<td>164.0 (62.2)</td>
<td>NA</td>
<td>147.5 (56.4)</td>
<td>.66</td>
</tr>
<tr>
<td>Diabetes-specific clinical characteristics, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>NA</td>
<td>19.3 (3.5)</td>
<td>NA</td>
<td>20.1 (3.4)</td>
<td>.77</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>NA</td>
<td>12.5 (5.2)</td>
<td>NA</td>
<td>12.8 (4.6)</td>
<td>.54</td>
</tr>
<tr>
<td>Glycerated hemoglobin, %</td>
<td>5.08 (0.33)</td>
<td>7.83 (1.35)</td>
<td>.001</td>
<td>6.70 (0.79)</td>
<td>.001</td>
</tr>
<tr>
<td>Lifetime average glycerated hemoglobin, %</td>
<td>NA</td>
<td>8.12 (1.16)</td>
<td>6.59 (0.38)</td>
<td>8.46 (0.99)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of hypoglycemic episodes</td>
<td>NA</td>
<td>4.46 (11.0)</td>
<td>NA</td>
<td>4.23 (10.5)</td>
<td>.92</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not available or not applicable.

<sup>a</sup>Group differences were tested by independent t tests for age, educational level, and lipid level and by χ² tests for sex composition, handedness, and race.

<sup>b</sup>Patients with type 1 diabetes were divided into good (within the treatment target range) and poor glycemic control subgroups according to the level of lifetime average glycerated hemoglobin. Patients with good glycemic control were defined as those with a lifetime average glycerated hemoglobin level less than 7%. Patients with poor glycemic control were defined as those with a lifetime average glycerated hemoglobin level of 7% or greater.

<sup>c</sup>Data were available in 119 patients with type 1 diabetes and 34 healthy comparison subjects.

<sup>d</sup>Blood glucose levels were measured at the time of imaging in a subsample (n = 45; 6 patients with good and 39 with poor glycemic control) of patients with type 1 diabetes.

**Table 2. Prefrontal Metabolite Concentrations and Ratios in Patients With Type 1 Diabetes Mellitus and Healthy Control Subjects<sup>a</sup>**

<table>
<thead>
<tr>
<th>Metabolite ratios</th>
<th>Normal</th>
<th>Good&lt;sup&gt;±&lt;/sup&gt;</th>
<th>Poor&lt;sup&gt;±&lt;/sup&gt;</th>
<th>P Value for Trend&lt;sup&gt;d&lt;/sup&gt;</th>
<th>All Diabetic Patients</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose:Cr</td>
<td>0.15 (0.05)</td>
<td>0.25 (0.12)</td>
<td>0.29 (0.15)</td>
<td>&lt;.001</td>
<td>0.28 (0.14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glx:Cr</td>
<td>1.23 (0.21)</td>
<td>1.34 (0.28)</td>
<td>1.38 (0.32)</td>
<td>.004</td>
<td>1.37 (0.31)</td>
<td>.004</td>
</tr>
<tr>
<td>NAA:Cr</td>
<td>1.06 (0.11)</td>
<td>1.07 (0.10)</td>
<td>1.06 (0.10)</td>
<td>.02</td>
<td>1.06 (0.10)</td>
<td>.65</td>
</tr>
<tr>
<td>Choline:Cr</td>
<td>0.24 (0.03)</td>
<td>0.24 (0.02)</td>
<td>0.24 (0.03)</td>
<td>.72</td>
<td>0.24 (0.03)</td>
<td>.03</td>
</tr>
<tr>
<td>Myo-inositol:Cr</td>
<td>0.55 (0.08)</td>
<td>0.58 (0.09)</td>
<td>0.57 (0.09)</td>
<td>.20</td>
<td>0.57 (0.09)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: Cr, creatine-phosphocreatine; Glx, glutamate–glutamine–γ-aminobutyric acid; NAA, N-acetyl aspartate–N-acetyl aspartyl glutamate.

<sup>a</sup>Data are mean (SD) values. Glucose measurements in 14 cases and Glx measurements in 5 cases were excluded due to poor spectral fit.

<sup>b</sup>Values were compared among the groups by means of analysis of covariance with a test for linear trend controlling for age, sex composition, and gray matter proportion.

<sup>c</sup>Values were compared between healthy control subjects and patients with type 1 diabetes mellitus by means of analysis of covariance with age, sex composition, and gray matter proportion as covariates.

<sup>d</sup>Data are values corrected for cerebrospinal fluid.
There were no significant differences in concentrations of other prefrontal metabolites, including Cr, choline, myo-inositol, or N-acetyl aspartate–N-acetyl aspartyl glutamate between adult T1DM and healthy control groups.

In addition to analyses using absolute metabolite concentrations, the same sets of analyses using ratios of each metabolite to Cr were conducted. Prefrontal glucose:Cr (F<sub>1,45</sub> = 26.42, P < .001) and Glx:Cr (F<sub>1,45</sub> = 8.55, P = .004) ratios were also higher in patients with T1DM than in healthy control subjects (Table 2). Positive linear trends between the level of lifetime glycemic control and of prefrontal glucose:Cr and Glx:Cr ratios were observed (P for trend < .001 and = .004, respectively).

Adult patients with T1DM showed substantially lower performances in 3 domains of cognitive function (memory function: effect size [ES] as defined by the adjusted mean difference in z scores, -0.65; P = .003; executive function: ES, -0.29; P = .01; and psychomotor speed: ES, -0.55; P < .001) relative to healthy control subjects. There was no difference in cognitive performance between the 2 T1DM subgroups. Detailed adjusted z scores of each neuropsychological test are summarized in eTable 4.

Multiple regression analysis showed that higher prefrontal Glx concentrations were associated with lower performance in global cognitive function (β [SE] = -0.11 [0.04], P = .002), and specifically in memory function (β [SE] = -0.23 [0.07], P = .001) and executive function (β [SE] = -0.07 [0.03], P = .045) among adult patients with T1DM. Each increase of 1 mmol/L in prefrontal Glx concentrations was associated with 0.23 ES lower performance in memory function and 0.07 ES lower performance in executive function in adult patients with T1DM (Figure 4). Prefrontal Glx concentrations in adult patients with T1DM were also positively correlated with Hamilton Depression Rating Scale scores (β [SE] = 0.51 [0.22], P = .02). The similar negative association between prefrontal Glx:Cr ratio and global cognitive function was observed in patients with T1DM (β [SE] = -0.53 [0.19], P = .007). Glx:Cr ratios were also associated with lower performance in memory and executive function (β [SE] = -1.04 [0.36], P = .005, and β [SE] = -0.43 [0.17], P = .02, respectively). A similar set of analyses was conducted with a subgroup of patients with T1DM who received the rapid-acting insulin analogues while covarying for insulin dose and time between insulin injections and MR imaging. Results from this subgroup analysis were similar to analyses with all patients with T1DM, although there were slight decreases in significance levels.

The negative associations between prefrontal Glx concentrations and cognitive function, however, were not observed in analyses of healthy control subjects. Multiple linear regression analysis using interaction terms confirmed that the effects of prefrontal Glx concentrations on cognitive function in adult patients with T1DM differed from those in healthy control subjects (P for interaction = .003, .046, and .001 for memory function, executive function, and global cognitive function, respectively; Figure 4). The pattern of associations between prefrontal Glx:Cr ratio and cognitive function also differed between groups (P for interaction = .005, .04, and .004 for memory function, executive function, and global cognitive function, respectively).

There were no significant associations between prefrontal glucose concentrations and cognitive function in adult patients with T1DM or healthy control subjects. However, an exploratory subgroup analysis including patients with T1DM (n = 58) with lifetime HbA<sub>1c</sub> levels of greater than 8% showed a negative association between prefrontal glucose concentrations and psychomotor speed (β [SE] = -0.27 [0.11], P = .02).

The present report documents that adult patients with T1DM have high prefrontal Glx levels and that higher prefrontal Glx levels are associated with lower performance in cognitive function and mild depression. Although low cognitive performance has been reported in some patients with T1DM, particularly those with long-term exposure to hyperglycemia, there is a less clear understanding regarding potential mediators for this CNS-related change. The present study may provide a new insight into its underlying pathophysiologic processes.
Glutamate, a primary excitatory neurotransmitter of the brain and a major component of the Glx spectrum, is a key molecule in the processes of learning and memory. When present beyond the capacity of glial uptake, however, glutamate accumulates extracellularly and has an excitotoxic effect on neurons. Differences between the effects of prefrontal glutamate on the cognitive function of healthy control subjects and on the cognitive function of our patients with T1DM, as we have noted, suggested that high prefrontal glutamate levels above the normal range in patients with T1DM may cause neurotoxic effects instead of serving as a substrate for neuronal plasticity. High prefrontal glutamate levels may in part explain the differential effects of prefrontal glutamate on the cognitive function of adult patients with T1DM and on the cognitive function of healthy control subjects.

Preclinical and clinical reports suggest that alterations in the synthesis and function of a family of neurotrophins may play an important role in several T1DM-related CNS changes. Considering the neurotrophins’ neuroprotective effects against glutamate-induced excitotoxicity, the altered function of neurotrophins in patients with T1DM may partly be responsible for the association between high prefrontal Glx levels and low cognitive performance in our T1DM cohort.

Although preventive optimal glycemic control, recommended for the reduction of T1DM-related complications, is likely to be beneficial in preventing decreases in cognitive performance, specific interventional treatments have not yet been suggested. Our finding regarding the relationship between high prefrontal glutamate levels and low cognitive performance may provide an insight into expanding treatment options. Drugs acting on

![Figure 4. Regression lines of prefrontal glutamate–glutamine–γ-aminobutyric acid (Glx) concentrations and estimated cognitive function in patients with type 1 diabetes mellitus (T1DM) (blue lines) and healthy control subjects (gray lines).](https://example.com/fig4.png)
homeostasis of the glutamatergic system may be of benefit in preventing low cognitive performance in patients with diabetes. \textsuperscript{49,50} Interestingly, N-methyl-D-aspartic acid receptor antagonists have recently been used in slowing cognitive decline in Alzheimer disease. \textsuperscript{23,31}

Prefrontal glucose levels, which were also higher in patients with T1DM, were not related to cognitive function in analyses of patients with T1DM and T1DM subgroups. Patients with more poorly controlled diabetes who have a lifetime average HbA\textsubscript{1c} level greater than 8%, however, showed a negative association between prefrontal glucose levels and cognitive function. This exploratory analysis indirectly suggests the presence of a threshold for glycemic control or a range of cerebral glucose levels at which cerebral glucose may directly affect cognitive function in patients with T1DM.

Depression affects up to 25% of patients with T1DM,\textsuperscript{6,7} increasing diabetic complications and mortality as well as decreasing overall quality of life.\textsuperscript{5,7} Although poor glycemic control is regarded as a risk factor for depression,\textsuperscript{6} its mechanism remains to be further clarified.\textsuperscript{7} Associations between dysregulated glutamatergic system and mild depressive symptoms, observed in the present study, may provide clues to uncovering a neurochemical mechanism of depression in T1DM. Because depression in patients with medical disorders is often resistant to standard treatments,\textsuperscript{32} alternative treatment options may be suggested in view of the current findings. Considering that the glutamatergic system has recently emerged as an important target for drug development, particularly in mood disorders with an atypical nature,\textsuperscript{33-35} drugs acting on the glutamatergic system, such as ketamine hydrochloride, lamotrigine, and riluzole,\textsuperscript{36} may have the potential to help improve depressive symptoms in patients with T1DM.

Our findings in patients with T1DM are different from those of a recent study on depressed patients with type 2 diabetes, which reported decreased Glx resonances in subcortical brain regions.\textsuperscript{37} This discrepancy may stem from several factors, including differences in sample characteristics, such as age, type of diabetes, comorbid medical conditions, and presence of current depression; in MRS methods used; and in brain regions examined.

In the present study, prefrontal Glx levels were 9.0% higher in patients with T1DM than in healthy control subjects, and they increased uniformly as the level of glycemic control worsened from normal through good to poor (4.2% and 1.0% of Glx level increment compared with healthy control subjects, respectively). A similar pattern of uniform increases in prefrontal glucose levels was observed.

We reasoned that sustained exposure to hyperglycemia would alter cerebral energy metabolism and change cerebral metabolite levels. Considering that high intracellular glucose concentrations lead to increased oxidative phosphorylation and, possibly, an accelerated glutamate-glutamine cycle,\textsuperscript{16} high prefrontal glutamate levels in patients with T1DM are likely to stem from increased de novo synthesis, ie, cellular adaptations to hyperglycemia. Preclinical evidence indicates that elevated glucose levels increase cerebral glutamate levels and that this link, ultimately, contributes to neuronal damage in diabetic as well as ischemic conditions.\textsuperscript{36,62} Data from the current study suggest that keeping glycemic control in the near-normal range is likely to help diabetic patients maintain optimal prefrontal glutamate levels, which may then reduce the risk of having lower cognitive performance.

High prefrontal Glx concentrations in patients with T1DM may be attributed in part to T1DM-specific conditions. Patients with T1DM frequently have antibodies to GAD,\textsuperscript{18,61} the rate-limiting enzyme that catalyzes the deamination of glutamate to \(\gamma\)-aminobutyric acid. These autoimmune abnormalities may lead to excessive glutamate accumulations.\textsuperscript{62} Consequently, patients with T1DM, especially those with high levels of GAD antibodies, may be vulnerable to glutamate-induced neuronal damage.

Patients with T1DM have been reported to have high cerebral myo-inositol levels.\textsuperscript{13,14} Considering myo-inositol’s function as an osmotic agent and a storage form for glucose,\textsuperscript{17,63-65} an increase in myo-inositol levels may reflect osmotic changes in the brain or inadequate glycemic control in patients with T1DM. Although there was no difference in prefrontal myo-inositol levels between subjects in our T1DM and control groups, patients with T1DM with a lifetime HbA\textsubscript{1c} level higher than 8% showed a higher myo-inositol:Cr ratio than healthy control subjects (\(F_1,93=4.41, P=.04\)). This is partly in accord with a previous report that suggested that myo-inositol may work as a cerebral osmolyte, particularly in diabetic patients with poor glycemic control.\textsuperscript{66}

Several potential confounding factors should be considered in interpreting our results. Although hyperglycemia-induced microvascular and macrovascular complications are relatively uncommon in patients before the age of 40 years,\textsuperscript{2} vascular injury in the brain may have contributed to the occurrence of low cognitive performance and depression. In our recent study, conducted with a similar but smaller T1DM cohort,\textsuperscript{32} however, we did not find an increased prevalence of brain T2 white matter hyperintensities, which are indirect markers of vascular injury. In addition, the relatively young ages (mean, 32.3 years) and short disease durations (mean, 19.9 years) of our patients with T1DM lessen the likelihood of the confounding by aging and cerebral vascular changes.

Although cognitive function in patients with T1DM may be influenced by previous severe hypoglycemic episodes,\textsuperscript{2} this association was not confirmed in a recent large-scale longitudinal trial.\textsuperscript{8,67} In the present study, the number or pattern of hypoglycemic episodes was not associated with cognitive function.

Mild ketosis, which frequently occurs in patients with T1DM,\textsuperscript{68-70} can influence cerebral glutamate metabolism. In cerebral ketone body metabolism, glutamate is transformed to \(\gamma\)-aminobutyric acid through the GAD pathway.\textsuperscript{71,72} Reduced GAD activity in patients with T1DM\textsuperscript{62} may further contribute to increases in cerebral glutamate levels.\textsuperscript{71,72}

Depressive symptoms in our patients with T1DM might be psychological responses to chronic medical disorders.\textsuperscript{73} Also, because our patients with T1DM had relatively mild depression and were not diagnosed as having clinical depression on the basis of the structured interview, our findings should not be generalized to diabetic patients with depression.

Our interpretation of high cerebral Glx levels as greater cerebral glutamate levels should be considered with caution.
tion given the potential overlapping of the chemical spectra of glutamate, glutamine, and γ-aminobutyric acid as Glx resonance at 1.5-T imaging.\(^{16,63,74}\)

Because plasma glucose levels were measured in a subset of patients with T1DM, the immediate effects of peripheral glucose levels cannot be effectively controlled in the present study assessing long-term effects of hyperglycemia on cerebral glucose metabolism (see eSupplement I for details). More controlled conditions, such as those using the experimental clamping technique during MR examination, would be necessary to accurately control for the confounding influence of the peripheral glucose levels—especially extreme hypoglycemia or hyperglycemia—on evaluating long-term cerebral metabolic changes in patients with T1DM.

The present MRS study, conducted with a large T1DM cohort, has shown that prefrontal Glx level is increased in adult patients with T1DM compared with healthy control subjects. Higher prefrontal Glx levels are associated with lower cognitive function and depressive symptoms in adult patients with T1DM. Randomized controlled studies are necessary to confirm the causal relationship between the level of glycemic control and cerebral glutamate changes.

Future studies are also recommended to evaluate the effectiveness of therapeutic options acting on glutamergic neurotransmission in the treatment or prevention of CNS-related changes in patients with T1DM.

In addition, our findings show that patients with T1DM who maintain glycemic control within the recommended treatment target of HbA\(_1c\) less than 7% would have the benefit of keeping optimal prefrontal glutamate levels, thereby potentially reducing the risk of CNS-related changes. A randomized clinical trial assessing the causal relationship between glycemic control and cerebral glutamate levels could confirm our interpretation.

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