Hyperglycemia Is a Stress Response in Acute Stroke

E. Woo, MRCP (UK), J.T.C. Ma, MRCP (UK), J.D. Robinson, MPhil, and Y.L. Yu, FRCPE

To explore further the relation between admission glucose concentration and outcome in stroke, we measured glucose, fructosamine, and glycosylated hemoglobin concentrations on admission in 216 patients seen within 24 hours after the onset of their first stroke. Fructosamine concentration reflects the degree of glycemia in the preceding 4–6 weeks and glycosylated hemoglobin concentration reflects that in the preceding 3 months. Based on clinical, computed tomographic, and necropsy findings, strokes were classified as cortical infarction, lacunar infarction, or intracerebral hemorrhage. Analyses were done including and excluding 47 diabetic patients. No correlation between neurologic outcome as mortality and fructosamine or glycosylated hemoglobin concentration was found. Survival showed a significant correlation with admission glucose concentration only for patients with intracerebral hemorrhage. Our results suggest that hyperglycemia is unlikely to worsen the outcome of acute stroke and that hyperglycemia probably represents either a latent diabetic state or a stress response. (Stroke 1988;19:1359–1364)

In the setting of acute stroke, is hyperglycemia a determinant of poor outcome or does it represent an acute response to stress? Glycosylated serum protein (fructosamine) and glycosylated hemoglobin (HbA1c) are known indexes of medium- and long-term exposure to blood glucose and have been used to monitor the degree of glycemic control in diabetic patients. As these measures are stable products not influenced by short-term fluctuations, they are superior to the admission glucose concentration as a clinical indicator of the glucose level at the onset of ischemia. If glucose concentration were an important determinant of ischemic brain injury, then fructosamine and HbA1c concentrations should show a correlation with outcome. We tested this hypothesis in our prospective study of 216 acute stroke patients.

Subjects and Methods

We included all stroke patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, during the 6 months from July to December 1986 in our study, provided they satisfied the following entry criteria: admission within 24 hours after the onset of ictus; blood glucose, fructosamine, and HbA1c concentrations determined immediately upon admission and before the administration of any intravenous fluid; diagnosis of stroke confirmed by computed tomography (CT) or necropsy; exclusion of other causes presenting with a stroke-like syndrome, such as subdural hematoma or epilepsy; and no prior neurologic disability from previous strokes or other diseases. CT was performed as soon as possible after admission and was repeated if the clinical features or the initial scan did not allow accurate classification.

We considered three subtypes of stroke: 1) cortical infarction (CI), ischemic stroke in patients with clinical evidence of cortical deficits and CT or necropsy evidence of recent cortical infarction including patients without cortical deficits in whom CT showed a subcortical lesion of >1.5 cm diameter; 2) lacunar infarction (LI), lacunar syndromes in patients without cortical deficits in whom CT was normal or showed a lucency characteristic of a lacune having a maximal diameter of ≤1.5 cm; 3) intracerebral hemorrhage (H), stroke caused by nontraumatic bleeding, primarily into the brain substance, with or without the presence of blood in the ventricles or the subarachnoid space.

We categorized patients for analysis: Category I included all patients satisfying the entry criteria irrespective of diabetic state and Category II excluded patients with a known history of diabetes mellitus, persistent hyperglycemia during the acute admission requiring insulin or oral hypoglycemic...
therapy, or a diabetic oral glucose tolerance test (OGTT) 3–6 months after ictus.

The degree of glycemic control was assessed by fructosamine and HbA₁ concentrations, which represent the time-averaged values for blood glucose over the preceding 4–6 weeks (for fructosamine) and 3 months (for HbA₁). Serum fructosamine was measured by colorimetric assay using the Abbott VP automated bichromatic analyzer (Abbott Laboratories Inc., Chicago, Illinois). The between-run coefficient of variation is 3% at 2.5 mmol/l fructosamine. HbA₁ was electrophoresed on agar gel using the Corning Electrophoresis System and quantified using the Corning M710 fluorimeter/densitometer (Corning Medical, Halstead, UK) with prior removal of the labile fraction by incubation with saponin reagent. The between-run coefficient of variation is 6% at 8% HbA₁. When HbA₁ exceeded 12%, the result was checked by affinity chromatography using Pierce prepacked Glyco Gel analytical columns and Pierce reagents (Pierce Chemical Co., Rockford, Illinois). The between-run coefficient of variation is 9%.

Standard 2-hour 75-g OGTTs were performed in all survivors 3–6 months after ictus following an overnight fast. Blood glucose was measured using Abbott hexokinase reagent and the Abbott VP automated bichromatic analyzer. Results were interpreted using criteria of the World Health Organization to distinguish diabetic from nondiabetic subjects.

Neurologic outcome was assessed by mortality at 1 week, 6 weeks, and 3 months.

Statistical analysis was performed with the aid of the Statistical Package for the Social Sciences (SPSS-X). Data were analyzed using Student’s two-tailed t test or the χ² test where appropriate. The probability value was adjusted for multiple comparisons.

Results

The total number of patients initially admitted was 229, but we excluded 13 from the study because of lack of CT or necropsy confirmation (in six), blood sampling >24 hours after the onset of ictus (in three), intravenous fluid administration before blood sampling (in three), and subdural hematoma (in one). The remaining 216 patients comprise Category I. The stroke subtype was confirmed by CT in 202 patients (93.5%) and by necropsy in the remaining 14 (6.5%). Of the 202 patients, CT was performed within 48 hours after onset of ictus in 61.9%, 3–7 days after onset of ictus in 16.8%, during the second week after onset of ictus in 15.4%, and during the third week after onset of ictus in the remaining 5.9%. CT was repeated 6–8 weeks after the ictus in 26 patients to accurately classify them as to stroke subtype.

Ten CI, 15 LI, and four H patients had a known history of diabetes mellitus. In addition, four CI, three LI, and 11 H patients were found to be diabetic on the basis of either persistent hyperglycemia during the acute admission or the OGTT performed 3–6 months after ictus. We excluded these 47 patients from Category I to form Category II. The demographics and the risk factor distribution for patients in Categories I and II are shown in Table 1.

CI patients had higher admission glucose concentrations than LI patients in both categories, while H patients consistently had the highest admission glucose concentrations irrespective of category. On the other hand, fructosamine and HbA₁ concentrations and the number of diabetics by history were not different among the three stroke subtypes.

Among Category I patients, there was a significant correlation between any two of glucose, fructosamine, and HbA₁ concentrations within each stroke subtype (Table 2). However, after exclusion of the diabetic patients, there was a significant correlation only between fructosamine and HbA₁ concentrations within each stroke subtype, and glucose concentration no longer showed any correlation with either fructosamine or HbA₁ concentration.

Table 1 shows the neurologic outcome for patients in both categories. Mortality was highest for H patients, especially at 1 week. CI patients had significantly higher mortality than LI patients. As only two LI patients died, no comparison of glycemic parameters in relation to mortality was made within this stroke subtype. CI and LI patients were combined into an ischemic stroke group for further analysis.

A comparison of glucose concentration by stroke subtype in relation to mortality shows that among patients with ischemic strokes, there was no difference in glucose concentrations between those who survived and those who died in either category (Figure 1). For H patients, admission glucose concentration was significantly higher in those who died than in those who survived in both categories.

Considering fructosamine concentration in relation to mortality, among patients with ischemic strokes, survivors generally had a higher concentration, although the difference did not reach significance in either category (Figure 2). For H patients, there was no difference in fructosamine concentrations between those who survived and those who died in either category.

While the trend among patients with ischemic strokes in Category I was for survivors to have higher HbA₁ concentrations, there was no significant difference between those who survived and those who died (Figure 3). Among Category II patients with ischemic strokes, survivors generally had lower HbA₁ concentrations although, again, the difference did not reach significance at any time after ictus. There was no correlation between HbA₁ concentration and mortality among the H patients in either category.

Discussion

Myers and Yamaguchi first noted the harmful effects of hyperglycemia in cerebral ischemia.
TABLE 1. Demographic Data, Risk Factor Distribution, and Neurologic Outcome for Patients in Categories I and II

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Cortical infarction</th>
<th>Lacunar infarction</th>
<th>Intracerebral hemorrhage</th>
<th>Cortical infarction</th>
<th>Lacunar infarction</th>
<th>Intracerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>73*</td>
<td>66†</td>
<td>77</td>
<td>59</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>% male</td>
<td>42.5</td>
<td>56.1</td>
<td>63.6</td>
<td>45.8</td>
<td>60.4</td>
<td>67.8</td>
</tr>
<tr>
<td>Mean ± SD age (yr)</td>
<td>67.5±9.7</td>
<td>65.5±10.9</td>
<td>67.4±9.3</td>
<td>66.9±9.9</td>
<td>65.4±11.1</td>
<td>67.6±9.6</td>
</tr>
</tbody>
</table>

Risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Category I (all patients)</th>
<th>Category II (nondiabetic patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% history of hypertension</td>
<td>42.5</td>
<td>39.0</td>
</tr>
<tr>
<td>% history of ischemic heart disease</td>
<td>13.7</td>
<td>16.9</td>
</tr>
<tr>
<td>% current smoker</td>
<td>28.8</td>
<td>32.2</td>
</tr>
<tr>
<td>% history of diabetes mellitus</td>
<td>13.7</td>
<td>0</td>
</tr>
<tr>
<td>Mean ± SEM hemoglobin (g/dl)</td>
<td>13.6±0.2</td>
<td>13.5±0.3</td>
</tr>
<tr>
<td>Mean ± SEM serum albumin (g/l)</td>
<td>44.5±1.6</td>
<td>45.1±1.5</td>
</tr>
<tr>
<td>Mean ± SEM glucose (mmol/l)</td>
<td>7.5±0.3</td>
<td>6.6±0.2</td>
</tr>
<tr>
<td>Mean ± SEM fructosamine (mmol/l)</td>
<td>2.2±0.1</td>
<td>2.1±0.1</td>
</tr>
<tr>
<td>Mean ± SEM HbA1 (%)</td>
<td>8.2±0.2</td>
<td>7.9±0.2</td>
</tr>
</tbody>
</table>

Neurologic outcome

<table>
<thead>
<tr>
<th>% mortality</th>
<th>1 week</th>
<th>6 weeks</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical infarction</td>
<td>8.28</td>
<td>26.0†</td>
<td>31.5%</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>0</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>35.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HbA1c, glycosylated hemoglobin.

*Includes 8 subcortical infarctions.
†46 pure motor hemiparesis, 12 sensorimotor stroke, 3 pure sensory stroke, 5 ataxic hemiparesis.
\(\chi^2\) compared with intracerebral hemorrhage.
\(\chi^2\) compared with lacunar infarction.

Administration of glucose to monkeys just before cardiac arrest markedly augmented the severity of brain injury. Their study was followed by further experimental evidence\(^{15-18}\) that glucose exerts a deleterious effect in cerebral ischemia, the mechanism of which is postulated to be severe tissue lactic acidosis.\(^{16,19}\) A number of clinical studies\(^{20-23}\) have shown a correlation between admission glucose levels in patients with acute cerebral infarction and neurologic outcome, consonant with the experimental studies, although there have been some reports to the contrary.\(^{1,24-26}\) A factor contributing to these conflicting results is the lumping of patients with CI and LI.\(^{26}\)

The major difficulty in clinical studies lies in interpreting the admission glucose concentration. This value may be influenced by a number of factors, including the stress of an acute medical illness.\(^{27,28}\) the interval between onset of the stroke and blood sampling, and any underlying illness, especially a latent diabetic state.\(^{29}\) To circumvent these difficulties, we limited our cohort to patients seen within 24 hours after the onset of ictus and performed OGTTs on all survivors in the chronic phase to search for latent diabetes mellitus. Most importantly, we examined fructosamine and HbA1c concentrations, which reflect the degree of glycemra before the onset of the stroke, to overcome the confounding effect of acute stress on the admission glucose concentration.

Although correlation between fructosamine concentration and stroke outcome has not been studied, the prognostic value of HbA1c concentration in stroke has been described.\(^{30-32}\) Oppenheimer et al\(^{10}\) employed random HbA1c concentrations and history to categorize diabetic status in 100 patients and

TABLE 2. Correlation Between Glucose, Fructosamine, and Glycosylated Hemoglobin Concentrations by Stroke Subtype

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>n</th>
<th>r</th>
<th>p</th>
<th>n</th>
<th>r</th>
<th>p</th>
<th>n</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category I (all patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>73</td>
<td>0.37</td>
<td>&lt;0.001</td>
<td>0.41</td>
<td>&lt;0.0001</td>
<td>0.63</td>
<td>&lt;0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>66</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>&lt;0.00001</td>
<td>0.63</td>
<td>&lt;0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>77</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.47</td>
<td>&lt;0.00001</td>
<td>0.49</td>
<td>&lt;0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category II (nondiabetic patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>59</td>
<td>0.17</td>
<td>NS</td>
<td>0.19</td>
<td>NS</td>
<td>0.46</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>48</td>
<td>0.19</td>
<td>NS</td>
<td>0.29</td>
<td>NS</td>
<td>0.47</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>62</td>
<td>0.13</td>
<td>NS</td>
<td>0.07</td>
<td>NS</td>
<td>0.32</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G, glucose; F, fructosamine; HbA1c, glycosylated hemoglobin; NS, not significant.
concluded that premorbid abnormal glucose tolerance was the major determinant of the hyperglycemic response to stroke. Cox and Lorains,31 in a prospective study of 109 patients, found that hyperglycemia with normal HbA1c concentration, which represents "stress" hyperglycemia, was associated with a poor prognosis. Neither study directly correlated HbA1c concentration with mortality, analyzed nondiabetics, or characterized the subtype of stroke.

We correlated fructosamine and HbA1c concentrations with outcome as stroke mortality, not only for all patients entered into our study, but also for a nondiabetic category that showed the same results. Among H patients (who had the highest mortality among the three stroke subtypes), admission glucose concentration best predicted outcome. For the group of ischemic strokes, CI patients had significantly higher mortality than LI patients and higher admission glucose concentrations, which reached significance in Category II. Fructosamine and HbA1c concentrations showed no correlation with outcome in any stroke subtype. The lack of correlation between these measures and outcome favors the argument that a high admission glucose concentration is the effect rather than the cause of a stroke.

Debate continues on whether a cyclic process exists in which stroke-induced stress causes hyperglycemia, which may in turn further extend the cerebral infarct. Some investigators have suggested that blood glucose levels should be maintained in the near-normal range in any patient with impending or evolving cerebral ischemia.20 Our data question the wisdom of such vigorous attempts, although avoiding glucose-containing infusions in the immediate treatment is justified. While we failed to confirm a causal role for hyperglycemia in stroke outcome, the admission glucose level still has prog-
Figure 3. Bar graphs of glycosylated hemoglobin (HbA\textsubscript{1c}) concentration in relation to mortality at 1 week, 6 weeks, and 3 months after ictus for cortical infarction (Cl), Cl and lacunar infarction (LI), and intracerebral hemorrhage (H) subtypes for Categories I and II. Number of patients is indicated at bottom of each column. Error bars show standard error of the mean. Open bars, survivors; shaded bars, dead.

Prognostic importance. Noting the actual interval between the onset of stroke and blood sampling for glucose determination and correlating these with outcome may shed further light on this important clinical question.

Acknowledgments

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