Admission Glucose Level in Relation to Mortality and Morbidity Outcome in 252 Stroke Patients

E. Woo, MRCP (UK), Y.W. Chan, MRCP (UK), Y.L. Yu, MRCP (UK), and C.Y. Huang, FRACP

In a prospective study to correlate admission glucose level with neurologic outcome in stroke, 252 acute stroke patients without prior disability and admitted within 24 hours of onset of ictus were assessed. The stroke was classified into one of three types — cortical infarct, lacunar infarct, or intracerebral hemorrhage — by clinical, computed tomographic, and necropsy findings. Fifty-one diabetic patients were excluded from the entire cohort to form a nondiabetic category for analysis. We found that admission glucose level showed a significantly higher degree of correlation with mortality and morbidity (measured as arm function, leg function, and activities of daily living) when cortical (n = 118) and lacunar (n = 58) infarcts were pooled compared with when they were assessed separately. For intracerebral hemorrhage (n = 76), admission glucose level correlated with mortality but not morbidity. This trend persisted despite exclusion of diabetic patients. These results are consistent with previous observations of a correlation between a high admission glucose level and the severity of stroke. The importance of segregating cortical from lacunar infarcts, two groups with a different natural history and prognosis, in any future analysis is emphasized. (Stroke 1988;19:185–191)

Epidemiologic data have shown that hyperglycemia is associated with an increased incidence of cerebrovascular diseases. Animal experiments using controlled degrees of cerebral ischemia have demonstrated that elevated blood glucose concentrations enhance the degree of neurologic deficit and morphologic brain damage. Clinical observations have also indicated that patients with hyperglycemia with or without diabetes mellitus have poorer neurologic outcome than their normoglycemic counterparts. The adverse effect of hyperglycemia on energy metabolism in the ischemic brain is postulated to be the result of severe lactic acidosis. On the other hand, cerebral blood flow studies indicate that hyperglycemia is not necessarily an unfavorable condition in acute cerebral ischemia. Moreover, in out-of-hospital cardiac arrests, a high glucose level may simply reflect prolonged cardiopulmonary resuscitation rather than be the primary determinant of poor neurologic outcome.

Such controversy prompted us to examine, in a prospective manner, the relation between admission glucose level and the outcome in a large cohort of stroke patients. We report our preliminary observations on 252 acute stroke patients admitted over the first 6 months of our study.

Subjects and Methods

A data bank was established in the Neurology Division, University Department of Medicine, Queen Mary Hospital in August 1985 to record pertinent information from all stroke patients admitted to the department. Any patient entered into the data bank is prospectively assessed at regular intervals during the acute phase of the illness and during the out-patient follow-up after discharge.

For the purposes of our study, all stroke patients admitted during the 6 months from August 1985 to February 1986 were included provided they satisfied the following entry criteria: 1) admission to the department within 24 hours of the onset of ictus; 2) plasma venous glucose level determined immediately upon admission before the administration of any intravenous fluids; 3) the diagnosis of stroke confirmed by computed tomography (CT) or necropsy; 4) exclusion of other causes that present with a stroke-like syndrome, e.g., subdural hematoma, epilepsy; and 5) no prior neurologic disability from previous strokes or neurologic or other diseases.

CT was performed as soon as possible after admission; it was repeated if the clinical features or the initial scan did not allow for accurate classification into the appropriate ischemic stroke type.

Definition of Stroke Types

We considered three types of stroke.

**Cortical infarct (CI).** Ischemic stroke with clinical evidence of cortical deficits (dysphasia, dyspraxia, visual field defects, gaze paresis) and CT or necropsy evidence of recent cortical infarction. Patients without cortical deficits but in whom CT showed a subcortical lesion >1.5 cm in diameter were included in this type.

**Lacunar infarct (LI).** Lacunar syndromes (pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, sensorimotor stroke) without cortical deficits. CT was normal or
showed a lucency characteristic of a lacune, the maximal diameter of which did not exceed 1.5 cm.

**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.

Apart from using CI, LI, and H stroke types independently in the analysis, CI and LI were combined to form an additional group (CI + LI) comprising all the ischemic strokes.

**Categorization of Patients**

In our analysis, patients were grouped into two categories: Category I, the "all-patient" category, which included all patients satisfying the entry criteria, irrespective of diabetic state or admission glucose level and Category II, the "non-diabetic" category, which was the same as Category I but excluded those patients with a known history of diabetes mellitus or an admission glucose level of >11.0 mM. This categorization is based on the World Health Organization criteria defining diabetes mellitus as likely in patients with a random plasma venous glucose level of >11.0 mM.

**Neurologic Assessment**

Every patient was assessed by one of two observers on Days 0, 1, 3, 7, 14, and 28, Week 6, and Month 3, or until death. For the purpose of the present analysis, neurologic outcome was assessed by mortality at 1 week, 6 weeks, and 3 months and by morbidity at 1 week, 6 weeks, and 3 months. Morbidity included arm function, leg function, and activities of daily living (ADL). Arm function was graded hierarchically into 1) normal, 2) fastens buttons/zips, 3) only holds a cup, or 4) no useful function. Grades 1 and 2 were considered good outcome, grades 3 and 4 poor outcome. Leg function was graded hierarchically into 1) normal, 2) climbs stairs, 3) walks on level ground, 4) stands without support, 5) stands with support, or 6) bed- or chair-bound. Grades 1, 2, and 3 were considered good outcome; grades 4, 5, and 6 poor outcome. ADL was scored according to the Barthel Index: 1) 100–81, independent; 2) 80–41, partially dependent; or 3) 40–0, totally dependent. ADL was assessed only at 6 weeks and 3 months.

**Statistical Methods**

Statistical analysis was performed with the aid of the Statistical Package for the Social Sciences (SPSS-X). Data were analyzed using Student's t test, χ², or analysis of variance (ANOVA) where appropriate.

**Results**

**Patients**

The analysis included 252 stroke patients who formed Category I. The demographic characteristics and risk factor distribution for patients in each stroke type are shown in Table 1. Stroke type was confirmed by CT in 242 patients (96%) and by necropsy in the remaining 10 (4%). Of the 242 patients who had CT confirmation, CT was performed within the first 48 hours in 60.2%, between 3 and 7 days in 14.3%, during the second week in 16.4%, and during the third week in the remaining 9.1%. CT was repeated 6–8 weeks after the ictus in 32 patients to classify them into the accurate ischemic type.

There were significantly more CI than LI patients with a known history of diabetes mellitus (17.8 vs. 5.2%, p<0.05, Table 1). Further, mean ± SEM glucose level on admission for CI patients was significantly higher than for LI patients (8.9 ± 0.6 vs. 7.1 ± 0.5 mM, p<0.025, Table 1).

Twenty-one CI, three LI, and seven H patients had a history of diabetes mellitus. In addition, ten CI, three LI, and seven H patients had an admission glucose level of >11.0 mM. All these patients were excluded from Category I to form Category II (Table 2). The demographic characteristics and the risk factor distribution for Category II patients are shown separately in Table 1.

**Neurologic Outcome**

The mortality and morbidity outcomes for each stroke type are shown in Table 3. Cortical infarcts had a significantly worse outcome compared with lacunar infarcts, whether measured in terms of mortality or morbidity in both categories of patients.

**Admission Glucose Level in Relation to Neurologic Outcome**

Mortality. Figure 1 illustrates the mean ± SEM admission glucose level for the patients who survived and those who died at 1 week, 6 weeks, and 3 months for CI, CI + LI, and H types in the two categories of patients. As only one LI patient died, no comparison was made within the LI group.

There was no significant difference in admission glucose level between those CI patients who survived and those who died at 1 week, 6 weeks, or 3 months in either category. However, when CI and LI patients were combined, admission glucose level was significantly higher in those who died at 6 weeks (p<0.05) in Category I and at 1 week (p<0.05) and 6 weeks (p<0.05) for Category II patients. Likewise, for H patients admission glucose level was significantly higher in the patients who died at 1 week (p<0.01), 6 weeks (p<0.005), or 3 months (p<0.0005) than in those who survived in both categories.

Morbidity — arm function. When CI patients were analyzed independently, admission glucose level was significantly higher only for those with a poor outcome at 3 months (p<0.05) in Category I (Figure 2). There was no difference at 1 week or 6 weeks, nor in Category II. Within LI patients, admission glucose level was not correlated with outcome. When CI and LI patients were pooled, there was a significant difference in admission glucose level with respect to outcome at 6 weeks (p<0.05) and 3 months (p<0.05) for Category I, and at 6 weeks (p<0.05) for Category II. In contrast to the ischemic strokes, H patients showed no correlation between outcome and admission glucose.

Morbidity — leg function. Within CI or LI patients, there was no correlation between admission glucose
and outcome for either category (Figure 3). When CI and LI patients were pooled, there was a significant difference in glucose level in relation to outcome at 1 week ($p<0.05$) for Category I and at 3 months ($p<0.05$) for Category II. As for arm function, H patients showed no correlation between outcome and admission glucose for leg function.

**Morbidity — activities of daily living.** Within CI patients who survived, there was no correlation between admission glucose level and ADL (Figure 4). For LI patients who survived, the totally dependent (ADL 40–0) group at 6 weeks within Category I had a significantly higher admission glucose level ($p<0.05$, ANOVA). When CI and LI patients were pooled, no significant correlation between admission glucose level and outcome was observed. Again for H patients, no correlation between admission glucose level and outcome could be observed.

**Discussion**

Our results show that the correlation between admission glucose level and neurologic outcome, whether measured by mortality or morbidity, was far more significant when cortical infarcts and lacunar infaracts were pooled compared with when they were assessed separately. This correlation persisted for the category of nondiabetic patients. We also showed that a high admission glucose level predicted mortality but not morbidity for intracerebral hemorrhage.

Our results can be criticized on several points. The first concerns our assessment of morbidity outcome. Here, apart from using the "gold standard," the Barthel Index, and dividing the score into three ranges according to standard recommendation, we also assessed two other indexes, arm function and leg function. Previous methods to measure arm function after stroke have either depended on special equipment or required time-consuming assessment. Such techniques cannot easily be applied in large-scale follow-up studies. We have therefore used a simple method on a wide range of patients. As the most essential function in the upper limb is fine precision grip of the hand, a patient's ability to fasten buttons/zip or better is therefore considered a good functional outcome. As for the lower limb, the ability to walk remains the most important function; our assessment of outcome follows the principle that being able to walk or better is considered good outcome whereas only being able to stand or worse is regarded as poor outcome.

Second, is our categorization of diabetic and non-diabetic patients accurate? As diabetic patients do poorly after a stroke, we chose to analyze a subgroup of patients who were nondiabetic to more accurately assess the effect of glucose in the absence of other confounding variables. However, there arose the inevitable situation in which some patients with a high glucose level died soon after admission, before they could be assessed for diabetic status. We therefore elected to use the World Health Organization criteria of a random glucose concentration of $\geq 11.0$ mM to define a diabetic. Among those patients without a history of diabetes mellitus, 20 met this criteria. Of these 20, three died within 48 hours of admission before their diabetic state could accurately be ascertained. The remaining 17 survived at least 1 week, during which time all had persistent hyperglycemia requiring anti-diabetic therapy. As for the remaining patients without any known history of diabetes and with an admission glucose level of $<11.0$ mM, during the follow-up period none developed biochemical or clinical evidence

**Table 1. Demographic Data and Risk Factor Distribution for Category I and II Patients**

<table>
<thead>
<tr>
<th></th>
<th>CI</th>
<th>LI</th>
<th>H</th>
<th>CI</th>
<th>LI</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>118*</td>
<td>58‡</td>
<td>76</td>
<td>87</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>46.6‡</td>
<td>65.5</td>
<td>55.3</td>
<td>55.2</td>
<td>67.3</td>
<td>53.2</td>
</tr>
<tr>
<td>Age (mean±SD years)</td>
<td>65.9±9.0</td>
<td>63.1±9.3</td>
<td>62.6±12.7</td>
<td>65.5±9.6</td>
<td>62.4±9.4</td>
<td>63.6±11.9</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>41.5</td>
<td>53.4</td>
<td>51.3</td>
<td>37.6</td>
<td>50.0</td>
<td>51.7</td>
</tr>
<tr>
<td>History of ischemic heart disease (%)</td>
<td>15.3</td>
<td>5.2</td>
<td>6.5</td>
<td>12.9</td>
<td>1.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>27.1</td>
<td>51.7$\dagger$</td>
<td>26.3</td>
<td>36.6</td>
<td>55.8</td>
<td>30.4‡</td>
</tr>
<tr>
<td>History of diabetes mellitus (%)</td>
<td>17.8$\ddagger$</td>
<td>5.2</td>
<td>9.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Admission glucose level (mean±SEM mM)</td>
<td>8.9±0.6$\ddagger$</td>
<td>7.1±0.5</td>
<td>7.9±0.4</td>
<td>6.7±0.2$#$</td>
<td>6.1±0.2</td>
<td>6.8±0.2$#$</td>
</tr>
</tbody>
</table>

*Including 10 subcortical infarcts.
†36 pure motor hemiparesis, 16 sensorimotor stroke, 4 pure sensory stroke, 2 ataxic hemiparesis.
\(p<0.05\) compared with LI ($\chi^2$).
\(p<0.01\) compared with H ($\chi^2$).
\(p<0.05\) compared with H ($\chi^2$).
\(p<0.025\), \#\(p<0.01\) compared with LI (Student's \(t\) test).

**Table 2. Patient Distribution in Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>CI</th>
<th>LI</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. All-patient category</td>
<td>118</td>
<td>58</td>
<td>76</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>21</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Admission glucose &gt;11.0 mM</td>
<td>10</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>II. Nondiabetic category</td>
<td>87</td>
<td>52</td>
<td>62</td>
</tr>
</tbody>
</table>

CI, cortical infarct; LI, lacunar infarct; H, intracerebral hemorrhage.
TABLE 3. Neurologic Outcome in Each Stroke Type

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Mortality (% dead) 1 week</th>
<th>6 weeks</th>
<th>3 months</th>
<th>Mobility (% poor) 1 week</th>
<th>6 weeks</th>
<th>3 months</th>
<th>ADL 1 week</th>
<th>6 weeks</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>14 (15)*</td>
<td>27 (25)*</td>
<td>32 (31)*</td>
<td>68 (68)*</td>
<td>50 (48)*</td>
<td>41 (40)*</td>
<td>65 (64)*</td>
<td>40 (43)*</td>
<td>35 (37)*</td>
</tr>
<tr>
<td>LI</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>45 (44)</td>
<td>23 (22)</td>
<td>19 (20)</td>
<td>38 (37)</td>
<td>12 (8)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>H</td>
<td>28 (29)</td>
<td>41 (44)</td>
<td>42 (45)</td>
<td>82 (84)</td>
<td>36 (31)</td>
<td>32 (26)</td>
<td>71 (75)</td>
<td>22 (23)</td>
<td>14 (15)</td>
</tr>
</tbody>
</table>

Outcome in percent. Category I (all patients) without parentheses; Category II (nondiabetic patients) within parentheses. CI, cortical infarct; LI, lacunar infarct; H, intracerebral hemorrhage. ADL, activities of daily living 80-41 and 40-0 groups.

*p<0.001, †p<0.005, ‡p<0.025 (χ²) compared with LI.

FIGURE 1. Admission glucose level in relation to mortality at 1 week, 6 weeks, and 3 months for cortical infarct (CI), CI+ lacunar infarct (LI), and intracerebral hemorrhage (H) types for Categories I and II. Number of patients indicated at bottom of each column. Error bars show SEM. Significance levels calculated using Student's t test (*p<0.05, **p<0.01, ***p<0.005). Open columns, alive; filled columns, dead.

FIGURE 2. Admission glucose level in relation to arm function at 1 week, 6 weeks, and 3 months for cortical infarct (CI), lacunar infarct (LI), CI+ LI, and intracerebral hemorrhage (H) types for Categories I and II. Number of patients indicated at bottom of each column. Error bars show SEM. Significance levels calculated using Student's t test (*p<0.05). Open columns, good outcome; filled columns, poor outcome.

Third, it should be noted that admission glucose level and certain aspects of morbidity were not without significant correlation when cortical strokes or lacunar strokes were analyzed individually. However, the
high glucose concentration and large ischemic injury, the detrimental effect of hyperglycemia on the ischemic penumbra could not be ascertained within the limits of our study. Perhaps by recruiting more patients and increasing the population size can one further elucidate the clinical interaction between hyperglycemia and ischemic stroke.

Our finding a correlation between admission glucose level and mortality in intracerebral hemorrhage is consistent with the NINCDS Stroke Data Bank experience that glucose level was strongly correlated with 30-day mortality for intracerebral hematoma. Our failure to find a correlation between admission glucose level and morbidity in intracerebral hemorrhage may be a Type II error due to the small number of patients who survived. Besides, the majority of survivors regained useful function of their extremities, further reducing the number of those with poor outcome. While these observations would favor the contention that hyperglycemia results from the stress of severe illness, the detrimental effects of high glucose concentration in the setting of intracerebral hemorrhage are again by no means excluded.

An increased stress response associated with a poor prognosis after stroke has been reported. Feibel et al., in studying 56 patients with cerebral infarcts and nine with subarachnoid hemorrhages, showed that greater mortality and eventual disability occurred in patients excreting >200 μg urinary norepinephrine and epinephrine daily early in the acute phase of the stroke. Melamed, in finding higher short-term mortality from ischemic infarct in patients who were hyperglycemic regardless of whether they were diabetic, suggested that hyperglycemia developed as a stress response in patients with more extensive brain damage. Likewise, Cox and Lorains showed increased mortality for those stroke patients with "stress" hyperglycemia, which was defined as hyperglycemia with a normal glycosylated hemoglobin (HbA1c).

The relation between hyperglycemia and stroke outcome remains complex. Experimental data have convincingly shown that glucose administration prior to cerebral ischemia seriously aggravates the postischemic neurologic outcome. Clinical studies have also shown a correlation between high glucose concentration and poor outcome, but the interpretation of such a finding is open to debate. It has been suggested that even modest elevations in blood glucose contributed to a worse outcome and that a high glucose concentration ought to be lowered to minimize ischemic damage. On the other hand, it was recently demonstrated, although in a global ischemic situation, that a high admission glucose level in patients with out-of-hospital cardiac arrest reflected a more difficult and prolonged resuscitation, and by itself glucose level was unlikely to be the major factor governing neurologic outcome. While our preliminary data also find a correlation between a high glucose concentration and a bad stroke, further research in this area is warranted to define more clearly the interaction between these two variables. A useful approach would be the measure-
ment of fructosamine and glycosylated hemoglobin, which reflect the degree of blood glucose regulation in the weeks and months, respectively, preceding the acute event. In addition, it is essential that cortical and lacunar strokes be segregated to ensure comparability with any future study.

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References


KEY WORDS • morbidity • mortality • glucose
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