Stress Hyperglycemia and Prognosis of Stroke in Nondiabetic and Diabetic Patients
A Systematic Overview

Sarah E. Capes, MD; Dereck Hunt, MD, MSc; Klas Malmberg, MD, PhD; Parbeen Pathak, BSc, MD; Hertzel C. Gerstein, MD, MSc

Background and Purpose—“Stress” hyperglycemia may be associated with increased mortality and poor recovery in diabetic and nondiabetic patients after stroke. A systematic review and meta-analysis of the literature relating acute poststroke glucose levels to the subsequent course were done to summarize and quantify this relationship.

Methods—A comprehensive literature search was done for cohort studies reporting mortality and/or functional recovery after stroke in relation to admission glucose level. Relative risks in hyperglycemic compared with normoglycemic patients with and without diabetes were calculated and meta-analyzed when possible.

Results—Thirty-two studies were identified; relative risks for prespecified outcomes were reported or could be calculated in 26 studies. After stroke of either subtype (ischemic or hemorrhagic), the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level >6 to 8 mmol/L (108 to 144 mg/dL) was 3.07 (95% CI, 2.50 to 3.79) in nondiabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients. After ischemic stroke, admission glucose level >6.1 to 7.0 mmol/L (110 to 126 mg/dL) was associated with increased risk of in-hospital or 30-day mortality in nondiabetic patients only (relative risk = 3.28; 95% CI, 2.32 to 4.64). After hemorrhagic stroke, admission hyperglycemia was not associated with higher mortality in either diabetic or nondiabetic patients. Nondiabetic stroke survivors whose admission glucose level was >6.7 to 8 mmol/L (121 to 144 mg/dL) also had a greater risk of poor functional recovery (relative risk = 1.41; 95% CI, 1.16 to 1.73).

Conclusions—Acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke in nondiabetic patients and increased risk of poor functional recovery in nondiabetic stroke survivors. (Stroke. 2001;32:2426-2432.)

Key Words: hyperglycemia • glucose • meta-analysis • prognosis • stroke

A high proportion of patients suffering an acute stress such as stroke1 or myocardial infarction2 may develop hyperglycemia, even in the absence of a preexisting diagnosis of diabetes. Both human and animal studies suggest that this is not a benign occurrence and that stress-induced hyperglycemia is associated with a high risk of mortality after both stroke3 and myocardial infarction.4 Moreover, recent evidence that glucose lowering with insulin reduces ischemic brain damage in animal models of stroke5 suggests that stress-induced hyperglycemia may be a modifiable risk factor for brain damage.

Despite these observations, the relationship between glucose levels and outcome after stroke in diabetic and nondiabetic patients has not been well characterized, and those studies that have examined this relationship have reported conflicting results. We therefore systematically reviewed the published literature to summarize the available evidence and to estimate the strength of the association between admission hyperglycemia and both short-term mortality and functional recovery after stroke.

Methods

Selection of Studies
A computerized literature search of MEDLINE (1966 to December 2000) was undertaken by 2 independent searchers, one of whom was assisted by a medical librarian experienced in literature searching. English-language articles reporting original data were eligible for inclusion in the study. Letters and review articles were perused for additional references but were not included in the meta-analysis. Search terms were obtained by noting recurrent words in the titles and abstracts of relevant articles known to the searchers. The subject headings blood glucose, stroke, cerebral infarction, cerebral hemorrhage, and cerebral ischemia and text words hyperglycemia, euglycemia, and hypoglycemia were combined with epidemiological terms (including the subject headings incidence, mortality, follow-up studies, cohort studies, and prognosis and text words natural history, course, and predict) in a strategy devised to maximize the sensitivity of the search.6

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From the Department of Medicine, McMaster University, Hamilton, Ontario, Canada (S.E.C., D.H., H.C.G.); Department of Cardiology, Karolinska Hospital, Stockholm, Sweden (K.M.); and William Osler Health Center, Toronto, Ontario, Canada (P.P.).
Reprint requests to Dr S.E. Capes, HHSC-McMaster Site, Room 3V51D, 1200 Main St W, Hamilton, Ontario L8N 3Z5, Canada. E-mail scapes@mcmaster.ca
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2426
In addition, a computerized search of Science Citation Index from 1980 to December 1999 was used to retrieve all articles citing any 1 of 7 key studies. Titles, abstracts, and/or the full text of articles retrieved from the Science Citation Index search were also assessed for relevance. The bibliographies of all relevant articles were searched by hand for additional articles, and experts in the field were contacted to identify any additional citations.

The full text of all articles thought to be potentially relevant by either of the 2 searchers was obtained. The authors and their institution, funding, the source of the article, and any acknowledgments were then deleted from all retrieved articles, and the resulting modified text was assessed independently for relevance by the 2 searchers.

An article was considered relevant to the overview if it was a cohort study or clinical trial of patients admitted with stroke, in which a baseline blood glucose level had been drawn within 24 hours of admission and in which outcomes (mortality within 1 month of the event or functional recovery from stroke) were reported according to the admission blood glucose level. Agreement between the 2 searchers on selection of relevant studies was measured, and any disagreements were resolved by consensus.

Inclusion and Exclusion Criteria
Studies retrieved by the literature search were included in the overview if they (1) assembled and prospectively followed an inception cohort, (2) explicitly stated that blood glucose was drawn within 24 hours of admission, (3) reported follow-up of ≥80% to hospital discharge or to 1 month, and (4) reported outcomes according to admission glucose level, as described above. Studies reporting exclusively on subarachnoid hemorrhage, transient ischemic attack, and nonstroke causes of focal neurological deficits were excluded. Studies that did not explicitly report the proportion of patients followed up or the timing of blood glucose measurement were also excluded.

Definition of Diabetes and Hyperglycemia
Patients were considered to be diabetic if they were classified as diabetic by the authors of the individual studies. The definition of hyperglycemia or “stress” hyperglycemia used was the one adopted by the authors of the individual studies and therefore varied from study to study.

Statistical Analysis
We calculated \( \kappa \) coefficients for agreement between the 2 observers on the inclusion of studies. The relative risk and 95% CI for mortality or functional recovery in hyperglycemic versus nonhyperglycemic patients after stroke were calculated for each study when possible. Relative risks were calculated separately for diabetic and nondiabetic patients when possible. The approach of DerSimonian and Laird\(^1\) (random-effects model) was used to generate a summary estimate of relative risk. Statistical heterogeneity among the studies was assessed by a \( \chi^2 \) test.

Results
Search Results
The 2 MEDLINE searches yielded 308 citations. From the titles and/or abstracts, 45 citations were thought to be potentially relevant by 1 or both of the reviewers (\( \kappa=0.93 \) for agreement between the 2 reviewers), and the full texts of these articles were retrieved. After review of the full text, 32 articles from the MEDLINE search were considered relevant (\( \kappa=0.78 \)). Two additional relevant articles were found by searching the bibliographies; the Science Citation Index search yielded 5 additional relevant articles.

Selection of Studies
Eight of 39 relevant articles were excluded from the final analysis because of methodological and reporting issues: the completeness of follow-up was not reported in 4 articles,\(^14\)–\(^17\) the timing of blood glucose measurement could not be determined in 2 articles,\(^8,19\) 1 article was excluded because patients formed part of a larger cohort reported in another article,\(^20\) and in 1 article the length of follow-up was insufficient to demonstrate the relevant outcomes (patients were followed for only 5 hours after stroke).\(^21\) Thirty-one articles describing 32 cohort studies (1 article described 2 separate cohorts\(^22\)) therefore were included in the overview.\(^1\)–\(^7\),\(^12\),\(^22\)–\(^45\)

Description of Studies
In 27 of the 32 studies, patients were enrolled and data were collected before outcomes had occurred. In the remainder, data were collected after outcomes had occurred. All of the included studies reported at least 80% complete follow-up to hospital discharge; 10 of the 32 studies also reported long-term follow-up (3 months to 1 year after stroke).\(^8,12,22,27,29–32,37\)

All studies included patients who had CT scan evidence of stroke and/or who met minimum World Health Organization criteria for the diagnosis of stroke (ie, rapidly developing focal neurological deficit lasting >24 hours or leading to death attributable to vascular causes\(^46\)). Four of the 32 studies presented data separately for patients with ischemic versus hemorrhagic stroke,\(^1,25,32,36\) and 11 studies included only patients with ischemic stroke (thromboembolic and/or lacunar).\(^6\) The remaining studies included only patients with hemorrhagic stroke,\(^34,40,42\) combined data for patients with ischemic and hemorrhagic stroke,\(^7\) or did not state the stroke subtype in included patients.\(^8,28\)

Functional recovery from stroke was reported in 13 of the 32 studies. The assessment was based on a validated scale (Barthel Index,\(^10,23,45\) Glasgow Outcome Scale,\(^37,45\) Canadian Stroke Scale,\(^24\) and Canadian Neurological Scale\(^25\)) in 6 of these studies. The remainder used the following qualitative descriptions of poor functional recovery: unable to return to any form of work,\(^7\) persistent disability,\(^26\) need for residential placement,\(^27\) dependent in activities of daily living,\(^11,22,28\) and stable deficit with no recovery.\(^29\)

Diabetes status was assigned on the basis of a history of diabetes or treatment with hypoglycemic agents in 20 of 32 studies;\(^‡\) in 8 studies, an elevated glycosylated hemoglobin\(^8,12,23,32,35,37\) or persistent or marked hyperglycemia\(^10,25\) was used to define diabetes. The definition of diabetes was not specified in 1 study,\(^28\) and 3 studies excluded patients with diabetes.\(^7,11,39\)

The definition of stress hyperglycemia also varied among studies. Most studies did not specify whether whole blood or plasma glucose was measured.\(^§\) Of those that did specify, 1 study measured whole blood glucose,\(^37\) and the rest measured plasma glucose levels. A random glucose level drawn on admission was used to define stress hyperglycemia in 10 of...
the 32 studies (with cutoffs ranging from 6 to 10 mmol/L [108 to 180 mg/dL]). Another 9 studies based the definition of stress hyperglycemia on fasting glucose level the morning after admission (ranging from 6.1 to 7.8 mmol/L [110 to 141 mg/dL]). Two of the 32 studies did not specify whether the glucose level used to define stress hyperglycemia in individual patients was random or fasting. The remaining 11 of 32 studies did not identify the glucose cutoffs used to define stress hyperglycemia; these studies reported either the mean glucose level in patients with good versus poor outcomes or the relationship between outcomes and glucose as a continuous variable on regression analysis.

### Relationship Between Admission Glucose Level and Outcomes

Table 1 shows the unadjusted relative risk of short-term mortality (before discharge from the hospital or within 1 month of stroke) associated with stress hyperglycemia after stroke of either subtype, which was calculated from data reported in 12 studies. In patients without diabetes, stress hyperglycemia was associated with a 3-fold increased risk of mortality after stroke (pooled relative risk, 3.07; 95% CI, 2.50 to 3.79). In patients with diabetes, stress hyperglycemia was not associated with a significantly higher risk of short-term mortality after stroke (pooled relative risk, 1.30; 95% CI, 0.49 to 3.43).

A planned exploratory analysis by stroke subtype was done. This analysis was restricted to 4 studies in which separate mortality data for ischemic and hemorrhagic stroke were reported. It included 682 patients with ischemic stroke (88 of whom were diabetic) and 98 patients with hemorrhagic stroke (9 of whom were diabetic). After ischemic stroke, nondiabetic patients with admission glucose level 6.1 to 7.0 mmol/L (110 to 126 mg/dL) had a 3.28-fold higher risk of short-term mortality (95% CI, 2.32 to 4.64). In patients with diabetes and ischemic stroke, the pooled relative risk associated with stress hyperglycemia was 2.00 (95% CI, 0.04 to 90.08). In contrast, stress hyperglycemia was not significantly associated with short-term mortality after hemorrhagic stroke. In nondiabetic patients, the relative risk of short-term mor-

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### TABLE 1. Relative Risk of In-Hospital or 30-Day Mortality Associated With Stress Hyperglycemia in Patients With Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Subtype</th>
<th>Definition of Stress Hyperglycemia, mmol/L</th>
<th>% of Pts With Stress Hyperglycemia</th>
<th>No. of Events/Pts at Risk</th>
<th>Unadjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melamed(^1)</td>
<td>TES, HS, SAH</td>
<td>&gt;6.7 (fasting)(^§)</td>
<td>35</td>
<td>58/108 36/205</td>
<td>3.06 (2.17–4.32)</td>
</tr>
<tr>
<td>Candelise(^9)</td>
<td>TES, HS</td>
<td>&gt;6.1 (fasting)</td>
<td>38</td>
<td>18/23 11/38</td>
<td>2.70 (1.57–4.65)</td>
</tr>
<tr>
<td>Gray(^22)</td>
<td>TES, HS</td>
<td>≥6 (random)</td>
<td>14</td>
<td>7/13 16/77</td>
<td>2.59 (1.33–5.04)</td>
</tr>
<tr>
<td>Woo(^23)*</td>
<td>TES, HS, LS</td>
<td>&gt;7.8 (fasting)</td>
<td>13</td>
<td>17/23 38/156</td>
<td>3.03 (2.10–4.38)</td>
</tr>
<tr>
<td>Toni(^25)*</td>
<td>TES</td>
<td>&gt;6.7 (fasting)</td>
<td>36</td>
<td>21/93 15/164</td>
<td>2.47 (1.34–4.55)</td>
</tr>
<tr>
<td>Liao(^32)</td>
<td>TES, HS, LS</td>
<td>≥7.0 (fasting)</td>
<td>30</td>
<td>5/16 1/38</td>
<td>11.88 (1.50–93.74)</td>
</tr>
<tr>
<td>Stig-Jørnsen(^33)*(^†)</td>
<td>TES, HS, LS</td>
<td>&gt;6 (random)</td>
<td>61</td>
<td>81/382 22/241</td>
<td>2.32 (1.49–3.62)</td>
</tr>
<tr>
<td>Cazzato(^36)*</td>
<td>TES, LS</td>
<td>&gt;6.1 (fasting)</td>
<td>63</td>
<td>15/37 2/22</td>
<td>4.46 (1.12–17.69)</td>
</tr>
<tr>
<td>Pooled relative risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.07 (2.50–3.79)</td>
</tr>
<tr>
<td>Melamed(^1)</td>
<td>TES, HS, SAH</td>
<td>&gt;6.7 (fasting)(^§)</td>
<td>78</td>
<td>22/62 0/17</td>
<td>12.86 (0.82–201.73)</td>
</tr>
<tr>
<td>Candelise(^9)</td>
<td>TES, HS</td>
<td>&gt;6.1 (fasting)</td>
<td>73</td>
<td>3/8 2/3</td>
<td>0.56 (0.17–1.87)</td>
</tr>
<tr>
<td>Gray(^22)</td>
<td>TES, HS</td>
<td>≥6 (random)</td>
<td>39</td>
<td>8/18 8/28</td>
<td>1.56 (0.71–3.40)</td>
</tr>
<tr>
<td>Liao(^32)</td>
<td>TES, HS, LS</td>
<td>≥7.0 (fasting)</td>
<td>83</td>
<td>1/15 0/3</td>
<td>0.75 (0.04–15.17)</td>
</tr>
<tr>
<td>Pooled relative risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.30 (0.49–3.43)</td>
</tr>
<tr>
<td>Matchar(^30)</td>
<td>TES</td>
<td>&gt;6.7 (random)</td>
<td>53</td>
<td>7/74 6/65</td>
<td>1.02 (0.36–2.89)</td>
</tr>
<tr>
<td>Sacco(^31)</td>
<td>TES, LS</td>
<td>&gt;7.8 (random)</td>
<td>39</td>
<td>17/123 8/193</td>
<td>3.33 (1.48–7.49)</td>
</tr>
<tr>
<td>Tuhrim(^34)</td>
<td>HS</td>
<td>&gt;10 (random)</td>
<td>N/A</td>
<td>0.44 0.24</td>
<td>1.83 (1.21–2.77)</td>
</tr>
<tr>
<td>Pooled relative risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.93 (1.15–3.24)</td>
</tr>
</tbody>
</table>

\(\text{Pts indicates patients; TES, thromboembolic stroke; HS, hemorrhagic stroke; SAH, subarachnoid hemorrhage; LS, lacunar stroke; and N/A, not available.}\)

*Unadjusted relative risks could not be calculated for diabetic patients in these cohorts because sufficient data were not reported.

\(\text{†Data read from bar graph.}\)

**Mortality data for diabetic and nondiabetic patients were not reported separately in these studies.}\)

\(\text{§Glucose had to fall by ≥1.1 mmol/L on follow-up to be classified as “reactive” or stress hyperglycemia in this study.}\)
tality after hemorrhagic stroke was 2.43 (95% CI, 0.68 to 8.73); there were insufficient data to calculate the corresponding relative risk in diabetic patients with hemorrhagic stroke.

The 10 studies that reported long-term mortality (3 months to 1 year) after stroke 8, 12, 22, 27, 29 – 32, 37 could not be pooled because they were statistically heterogeneous ($P < 0.05$ for homogeneity). These studies combined data for diabetic and nondiabetic patients, and many included patients with both hemorrhagic and ischemic stroke. The studies differed in duration of follow-up, number of diabetic patients, and number of patients with each stroke subtype. Stress hyperglycemia was associated with a significantly increased risk of long-term mortality in 5 of these 10 studies 12, 22, 27, 31, 32 (data not shown).

Table 2 shows the unadjusted relative risk of poor functional recovery associated with stress hyperglycemia, which could be calculated from data in 8 studies. 7, 22, 23, 25 – 27, 29, 37 Stress hyperglycemia on admission was associated with poor functional recovery up to 6 months after stroke in nondiabetic patients (pooled unadjusted relative risk of poor functional recovery = 1.41; 95% CI, 1.16 to 1.73). Data on stroke recovery in diabetic patients were not reported.

Twelve of the 32 studies did not report sufficient data to allow calculation of the unadjusted relative risk of outcomes in patients with and without stress hyperglycemia. Data from these studies therefore could not be included in the quantitative meta-analysis. Six of these 12 studies performed a multivariate analysis to explore the relationship between glucose level and poor outcomes. The largest of these 12 studies analyzed data from a stroke registry that included 1776 patients with ischemic stroke and 355 patients with hemorrhagic stroke, 83% of whom were nondiabetic. In both

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Subtype</th>
<th>Definition of Stress Hyperglycemia, mmol/L</th>
<th>No. of Events/Pts at Risk</th>
<th>Unadjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pulsinelli*</td>
<td>TES</td>
<td>&gt;6.7 (random)</td>
<td>8/14</td>
<td>4/17</td>
</tr>
<tr>
<td>Woo23*</td>
<td>TES, HS, LS</td>
<td>&gt;7.8 (fasting)</td>
<td>1/5</td>
<td>20/100</td>
</tr>
<tr>
<td>Toni25*</td>
<td>TES</td>
<td>&gt;6.7 (fasting)</td>
<td>42/72</td>
<td>66/149</td>
</tr>
<tr>
<td>Kushner26*</td>
<td>TES</td>
<td>&gt;6.8 (random)</td>
<td>5/11</td>
<td>3/11</td>
</tr>
<tr>
<td>Weir27</td>
<td>TES, HS, LS</td>
<td>&gt;8 (fasting or random)</td>
<td>27/95</td>
<td>102/475</td>
</tr>
<tr>
<td>van Kooten37*</td>
<td>TES, HS, TIA</td>
<td>≥6.7 (fasting) or ≥8 (random)</td>
<td>7/15</td>
<td>8/46‡</td>
</tr>
<tr>
<td>Pooled relative risk</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Studies reporting data for diabetic patients

No data

Studies reporting data for diabetic and nondiabetic patients combined‡

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Subtype</th>
<th>Definition of Stress Hyperglycemia, mmol/L</th>
<th>No. of Events/Pts at Risk</th>
<th>Unadjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power22</td>
<td>TES</td>
<td>&gt;7.0 (random)</td>
<td>10/24</td>
<td>22/78</td>
</tr>
<tr>
<td>Adams29</td>
<td>TES, LS</td>
<td>&gt;7.2 (random)</td>
<td>2/30</td>
<td>4/28</td>
</tr>
<tr>
<td>Pooled relative risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations are as defined in Table 1. TIA indicates transient ischemic attack.

*Unadjusted relative risks could not be calculated for diabetic patients in these cohorts because sufficient data were not reported.

†Data for diabetic and nondiabetic patients were not reported separately in these studies.

‡May include some undiagnosed diabetic patients (ie, patients without a history of diabetes but with elevated HbA1c).
stroke subtypes combined, admission glucose level was a significant predictor of mortality independent of other prognostic factors (odds ratio = 1.007; 95% CI, 1.004 to 1.01). Another large study included 1259 patients with ischemic stroke (71% of whom were nondiabetic) enrolled in a clinical trial of a low-molecular-weight heparinoid versus placebo. It showed that the odds of a poor functional recovery at 3 months increased by 22% for each 100-mg/dL increase in admission glucose level after adjustment for confounders (P = 0.03). Of the 4 smaller studies performing multivariate analyses, 1 found glucose level to be an independent predictor of mortality in patients with ischemic stroke. I enrolled only patients with hemorrhagic stroke and did not show this association, and the other 2 studies did not identify glucose level as an independent predictor of mortality at 30 days or 3 months in a mixed population of patients with ischemic and hemorrhagic stroke. The remaining 6 of the 12 studies reported only the mean glucose level in patients with a poor outcome (death or poor functional recovery) compared with those with a good outcome. Patients who experienced a poor outcome tended to have higher glucose levels than those with a good outcome.

Discussion

This systematic overview shows that in patients with no history of diabetes who have an ischemic stroke, even moderately elevated glucose levels are associated with both a 3-fold higher risk of short-term mortality and an increased risk of poor functional recovery compared with lower glucose levels. This finding is supported by studies showing higher mean admission glucose level in nonsurvivors of stroke compared with survivors. It is also supported by multivariate analyses of data from 2 large studies, in which admission glucose level was a significant predictor of mortality or poor functional recovery after stroke independent of other prognostic factors.

Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke. First, hyperglycemia may be directly toxic to the ischemic brain. Although the mechanism is not fully understood, accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) may contribute. Intracellular acidosis may promote and accelerate ischemic injury by enhancing lipid peroxidation and free radical formation, allowing accumulation of intracellular calcium (a key component of the glutamate-dependent excitotoxicity seen in ischemic neurons), and impairing mitochondrial function. These neurotoxic effects may be particularly important in the ischemic penumbra (the region of brain tissue surrounding the core of infarcted tissue where neurons are injured but still viable). Indeed, in an animal model of stroke, hyperglycemia facilitated the development of cellular acidosis in the ischemic penumbra and resulted in a greater infarct volume compared with insulin-treated hypoglycemic animals. Thus, hyperglycemia may promote the recruitment of potentially salvageable neurons into the infarction.

Second, hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation and, in hyperglycemic patients with acute myocardial infarction, have been shown to promote calcium overload and arrhythmias; however, the effect of excessive circulating free fatty acids on ischemic brain has not been studied.

Third, patients without a diagnosis of diabetes who develop stress hyperglycemia are likely to have dysglycemia (ie, blood glucose level above the normal range but below the threshold for diabetes) or undiagnosed diabetes when not stressed. Patients with dysglycemia or undiagnosed diabetes have a higher risk of vascular disease than patients with normal blood glucose level. These patients could sustain more ischemic damage at the time of infarction as a result of more extensive underlying cerebral vasculopathy compared with those who do not develop stress hyperglycemia. Although the extent of cerebral atherosclerosis in patients with and without stress hyperglycemia has not been studied, hyperglycemia may be an important determinant of the widespread changes in both small cerebral blood vessels and large extracranial vessels seen in diabetic patients. Furthermore, even nondiabetic-range hyperglycemia is associated with endothelial dysfunction, another potential mechanism of cerebrovascular disease in these patients. Patients with dysglycemia or undiagnosed diabetes may also have a higher risk of cardiac events after stroke; however, the available evidence suggests that most of the excess mortality in patients with stress hyperglycemia is due to the neurological effect of the large stroke and not to a higher fatal cardiac event rate.

Fourth, hyperglycemia may disrupt the blood-brain barrier and promote hemorrhagic infarct conversion. Consistent with this possibility is the observation that in 138 diabetic and nondiabetic patients with ischemic stroke treated with intravenous recombinant tissue plasminogen activator, higher admission serum glucose level was associated with a higher risk of hemorrhagic conversion of the infarct, with a substantial increase in risk with levels > 8.4 mmol/L. This study did not report mortality or functional recovery from stroke in relation to admission glucose level and therefore was not included in this overview. Only 1 study included in the overview reported the risk of hemorrhagic infarct conversion in relation to glucose level. This study followed 1259 patients with ischemic stroke randomized to a low-molecular-weight heparinoid versus placebo; in the 2 groups combined, there was no association between admission glucose level and risk of hemorrhagic infarct conversion. The reason for the discrepancy between these 2 studies is not clear.

Fifth, stress hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke. For example, patients with severe or fatal strokes might develop hyperglycemia because of greater release of “stress hormones” such as cortisol and norepinephrine. Indeed, a logistic regression analysis of data from 345 patients with stroke showed that the strength of the positive association between hyperglycemia and mortality lessened after accounting for the severity of stroke (as indicated by decreased level of consciousness and weakness score at the onset of stroke). However, animal
studies showing that administration of insulin reduces the size of the infarct and improves prognosis after stroke strongly support the view that stress hyperglycemia is of pathophysiological significance in patients with stroke and is not simply an epiphenomenon of the stress response to stroke. Whereas many studies have shown that diabetes increases the risk of mortality after stroke, few have explored the relationship between admission hyperglycemia and prognosis after stroke in diabetic patients. This review did not find evidence that admission hyperglycemia increases the risk of mortality within a month of ischemic stroke in diabetic patients. The discrepancy between this finding and the strong association between stress hyperglycemia and mortality in nondiabetic patients with ischemic stroke may be due to several reasons. First, the number of diabetic patients in the studies included in this overview was small, resulting in low power to detect the same relative risk in diabetic patients as in nondiabetic patients. Second, the threshold values that defined hyperglycemia in the individual studies may have been too low to distinguish between diabetic patients with and without stress hyperglycemia. Third, the definition of stress hyperglycemia is intrinsically problematic in diabetic patients because the unstressed baseline level of glucose is not known. Fourth, diabetic patients are more likely to receive therapy for hyperglycemia. Glucose-lowering therapy would reduce the amount of glucose available to diffuse into brain and might reduce cerebral lactic acidosis and other harmful metabolic changes in the brain. Furthermore, if insulin was used, this might also limit the extent of the infarct through anticoagulant effects such as reduced thromboxane production and decreased plasminogen activator inhibitor-1 activity. The use of glucose-lowering therapy (including insulin) in patients with stress hyperglycemia could not be assessed in the studies included in this overview.

The results of this overview are limited by several factors: the pooled studies differed in inclusion and exclusion criteria, definition of hyperglycemia, and concomitant treatment; relative risks included in the meta-analysis were not adjusted for other prognostic factors; and only published studies were included. Nevertheless, the strong and consistent association between admission hyperglycemia and poor prognosis after stroke observed in nondiabetic patients suggests that glucose level is an important risk factor for morbidity and mortality after stroke. These results highlight the need for further research to determine whether glucose lowering at the time of stroke can improve outcomes; at least 1 clinical trial to address this question is already under way.

References


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