original article

Impact of hyperglycemia on ischemic stroke mortality in diabetic and non-diabetic patients

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BACKGROUND: Previous studies suggest that infarct expansion may be responsible for increased mortality after stroke onset in patients with prolonged stress hyperglycemia. Therefore, we evaluated the influence of prolonged stress hyperglycemia on stroke mortality in patients with and without diabetes.
PATIENTS AND METHODS: For 630 stroke patients admitted to the neurological intensive care department within 24 hours of stroke onset, we correlated mean blood glucose levels (MBGL) at admission and 72 hours after admission in diabetic and non-diabetic patients with final outcome. Blood glucose levels higher then 6.1 mmol/L (121 mg/dL) were treated as hyperglycemia.
RESULTS: Of 630 patients (mean age 71 ± 6), 410 were non-diabetic (mortality, 25%) and 220 patients were diabetic (mortality, 20%). All patients who died within 28 days of hospitalization had prolonged hyperglycemia (at admission and after 72 hours, despite insulin therapy). The unadjusted relative risk of in-hospital mortality within 28 days for all stroke patients was 0.68 (95% CI, 0.14-1.9) for non-diabetic patients and 0.39 (95% CI, 0.27-1.56) for diabetic patients. The unadjusted relative risk of in-hospital mortality within 28 days in ischemic stroke in patients with MBGL > 6.1-8.0 mmol/L (121-144 mg/dL) at admission and after 72 hours was 1.83 (95% CI, 0.41-5.5) for non-diabetic patients and 1.13 (95% CI, 0.78-4.5) for diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 times higher relative risk of in-hospital 28-day mortality than patients with diabetes.
CONCLUSION: Prolonged stress hyperglycemia in ischemic stroke patients increases the risk of in-hospital 28-day mortality, especially in non-diabetic patients.

Stroke is leading cause of disability and death in developed countries. Therefore it is of great interest to evaluate all factors that could affect the acute phase of stroke and change 30-day mortality and functional outcome. One of these factors is prolonged stress hyperglycemia, which is still not exactly defined and possibly not well treated.[1-3]

Hyperglycemia (blood glucose level >6.1mmol/L or 121 mg/dL) is common in early phase of stroke, even in patients without a previous diagnosis of diabetes mellitus. It has been found in two thirds of all stroke patients and in almost half of ischemic stroke patients.[3,4] A recent meta-analyses of prospective and case-control studies confirmed the importance of early stress hyperglycemia as a predictor of stroke outcome, but debate continues as to whether the effect is independent of pre-existing diagnosis of diabetes or initial stroke severity. It is still not clear what cut-off value of the mean blood glucose level (MBGL) should be considered safe in diabetic and non-diabetic patients.[5] New and sophisticated techniques such as MR spectroscopy, CT, PET and conventional MRI findings still have inconclusive results.[6] Therefore we evaluated data on stroke patients admitted to the Neurological Intensive Care Department to estimate the influence of prolonged stress hyperglycemia on short-term mortality in both diabetic and non-diabetic patients.

PATIENTS AND METHODS

We included the data of 630 stroke patients admitted to the Neurological Intensive Care Department within 24 hours of stroke onset in the year 1999 (according to previous medical documentation). The standardized workup for stroke included: blood hematology and chemistry, blood cholesterol and glucose levels, electrocardiography (ECG), chest X-ray, carotid and vertebral color Doppler flow imaging (CDFI) and transcranial Doppler (TCD), brain computed tomography (brain CT), angiography and spinal tap with cerebrospinal fluid (CSF) analyses in selected patients

The definition of stroke (according to WHO criteria) was "rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours, unless interrupted by surgery or death, with no apparent cause other than a vascular origin". By definition, patients with transient ischemic attacks were excluded. The criterion for stroke classified as ischemic stroke or intracerebral hemorrhage was verification of the clinical picture on a brain CT scan or spinal tap. Short-term 30-day case fatality was counted as the proportion of deaths in hospitalized stroke patients. Blood glucose levels at admission and during next 72 hours that were higher than 6.1 mmol/L (121 mg/dL) were treated as hyperglycemia.

Data are presented as absolute numbers (expressed as mean ± SD) and percentages. Statistical analysis was performed with StatSoft Inc for Windows. Proportions were used in most tables and figures. The unadjusted relative risk and 95% confidence interval for mortality in all stroke patients and in ischemic and hemorrhagic stroke patients separately in hyperglycemic versus non-hyperglycemic patients, and hyperglycemic diabetic and non-diabetic patients was calculated. χ^2 test was used to test differences in proportions. Statistically significant values were considered for $P<0.05$ and $P<0.01$.

RESULTS

There were 630 patients (mean age, 73±15.6 years), including 267 men (mean age, 72±14.8 years) and 363 women (75±16.3) admitted to the Neurological Intensive Care Department in the year 1999. Women were 5 years older, but there were no statistically significant differences according to age in the patients with stress hyperglycemia.

Crude 30-day short-term mortality was 26% (164 patients), while 30-day short-term mortality in patients with stress hyperglycemia versus patients without stress hyperglycemia was 25% in non-diabetic patients and 20% in diabetic patients. There were 101 non-diabetic patients (16% of all patients) with stress hyperglycemia that died within 30 days of hospitalization versus 46 patients with pre-existing diabetes who died within 30 days (7% of all patients). There were more than double number of non-diabetic patients versus diabetic patients who died with verified stress hyperglycemia. Statistically significant sex differences were not found so we pooled the data.

There was no statistically significant difference in MBGL between non-diabetic patients and diabetic patients who did not have stress hyperglycemia and who recovered after stroke. In the group of patients with stress hyperglycemia who died within 30 days of hospitalization there were statistically significant differences in MBGL between the non-diabetic patients and the diabetic patients. The first group had a lower MBGL at admission and after 72 hours ($P<0.05$). Patients in both groups (diabetic and non-diabetic) varied in MBGL (6.1-36 mmol/L at admission, 6.1-24 mmol/L after 72 hours), but most of them (in both groups) had a MBGL between 6.1-8.0 mmol/L (121-144 mg/dL).

The unadjusted relative risk of in-hospital mortality within 30 days for all stroke patients was 0.68 (95% CI, 0.14-1.9) for non-diabetic patients and 0.39 (95% CI. 0.27-1.56) for diabetic patients (Figure 1). The un-

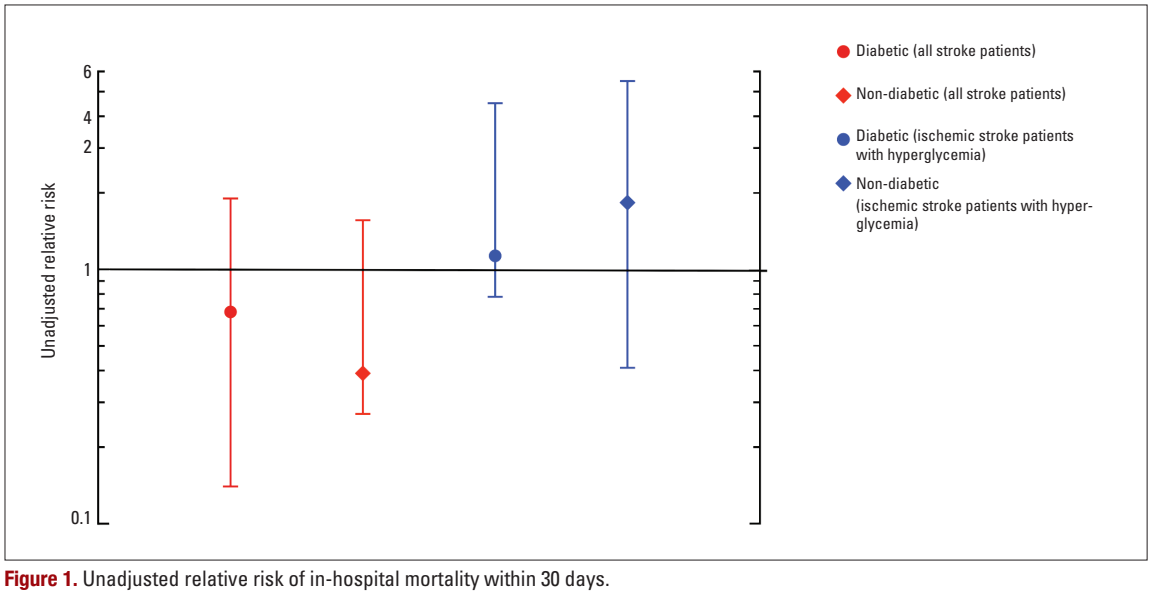

Figure 1. Unadjusted relative risk of in-hospital mortality within 30 days.

adjusted relative risk of in-hospital mortality within 30 days in ischemic stroke patients with MBGL >6.1-8.0 mmol/L (121-144 mg/dL) at admission and after 72 hours was 1.83 (95% CI, 0.41-5.5) for non-diabetic patients and 1.13 (95% CI, 0.78-4.5) for diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 higher relative risk of in-hospital 30-day mortality than diabetic patients.

DISCUSSION

There are multiple mechanisms of the neuronal damage and blood-brain dysfunction in patients with prolonged stress hyperglycemia. Elevated blood glucose is common in the early phase of stroke and is probably mediated by the increased release of the "stress hormones"–cortisol and epinephrine.

Relative insulin deficiency associated with increased lipolysis associated with hyperglycemia diminishes cerebrovascular reactivity. Even in nondiabetic patients stress hyperglycemia may be a marker of deficient glucose regulation in individuals with insulin resistance and developing diabetes mellitus.[7] By provoking anaerobic metabolism, lactic acidosis, calcium overload, decreased mitochondrial function and free radical production, hyperglycemia may be a cause of the direct membrane lipid peroxidation and cell lysis in the zone of the numbra and penumbra, leading to the direct death of neurons and dysfunction of the blood-brain barrier and promoting hemorrhagic infarct conversion. Also, insulin resistance is a very well known indirect risk factor for stroke onset due to increased thrombophilia, endothelial dysfunction and inflammation.[8]

Progression of ischemic tissue damage is accompanied by increased glutamate secretion and decreased gamma-aminobutyric acid, mediating the spreading depression of neuronal activity.[8] There is increased activity of neuronal endonucleases and activation of the enzymes of the arachidonic acid cycle-cyclooxigenase-2 and 5-lypoxigenase in the first 24 hours. These enzymes are rate-limiting enzymes in arachidonic acid metabolism, leading to production of prostacyclin E2(PGE2) and cysteine-leukotrienes (cys-LTs), which are highly potent cerebral vasoconstrictors that lead to enhanced vascular permeability, which induces formation of vasogenic edema.[9]

Recent MRI studies have confirmed the correlation of penumbral tissue loss and elevated blood glucose levels. Using a subcutaneous glucose sensor for 72 hours of glucose monitoring, there was strong evidence of a link between infarct expansion and hyperglycemia, suggesting that hyperglycemia not only determines the initial infarct volume, but also the infarct volume enlargement.[6]

Previous clinical trials have shown that hyperglycemia at admission is correlated with a worsened clinical outcome. In non-diabetic patients stress hyperglycemia was associated with a 3-fold risk for fatal stroke at 30 days and a 1.4-fold risk for poor functional outcome as compared with normoglycemic patients.[11-14] In several thrombolysis trials, hyperglycemia has been found to be associated with decreased odds for neurological improvement and also with increased secondary hemorrhagic events, which leads to speculation that hyperglycemia might be partially responsible for the diminishing beneficial effect of rtPA and early reperfusion.[15,16]

In our study we have shown that there is an unadjusted relative risk of in-hospital mortality within 30 days of 0.68 (95% CI, 0.14-1.9) in nondiabetic patients and of 0.39 (95% CI, 0.22 -1.56) in diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 higher relative risk of in-hospital 28-day mortality than diabetic patients, which correlates with previous studies showing a relative risk about 2.0 times higher in non-diabetic patients than diabetic patients.[11-14]

All patients who died within 30 days (diabetic and non-diabetic) varied in MBGL (6.1-36 mmol/L at admission, 6.1-24 mmol/L after 72 hours), but most of them (in both groups) had an MBGL between 6.1-8.0 mmol/L (121-144 mg/dL), which confirms that it is not only important to reduce extremely high MBGL, but also to regulate the moderate hyperglycemia (similar to the results of the Glucose Insulin in Stroke Trial-GIST-UK).[12]

The results of this study are limited because relative risk was not adjusted for other risk factors but despite that, a strong and consistent association between admission and 72 hours prolonged hyperglycemia and increased 30-day stroke mortality, especially in non-diabetic patients suggests that not only high but also moderate hyperglycemia is an important risk factor affecting stroke outcome.[11-14] Our results once again demonstrate the need for systematic clinical studies to encourage the restoration of normoglycemia in the acute phase of stroke, with or without applying thrombolysis and/or neuroprotectives in both non-diabetic and diabetic patients.[15,16] The European Stroke Initiative (EUSI) and American Stroke Association (ASA) would need to reconsider their guidelines (EUSI MBGL<10mmol/L, ASA <16.63 mmol/L), so as to reduce 30-day stroke mortality and improve functional outcome.

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