Dynamic of Hyperglycemia as a Predictor of Stroke Outcome in the ECASS-II Trial

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Background and Purpose—Baseline hyperglycemia has been considered an independent predictor of stroke outcome. The present study analyzes the dynamics of serum glucose levels within the first 24 hours and its impact on stroke outcome.

Methods—We studied 748 patients with acute ischemic hemispheric stroke in the second European Cooperative Acute Stroke Study (ECASS-II). The patients had 2 serum glucose measurements, at baseline and at 24 hours. Four dynamic patterns were defined as baseline hyperglycemia present only at baseline, 24-hour hyperglycemia present only at 24 hours, persistent hyperglycemia, ie, hyperglycemia at baseline and at 24 hours, and persistent normoglycemia, ie, normoglycemia at baseline and at 24 hours. The end points were 7-day neurological improvement on National Institutes of Health Stroke Scale, 30-day favorable functional outcome (Barthel Index 95 or 100), 90-day negligible dependence (modified Rankin Scale 0 to 2), all-cause mortality within 90 days, and hemorrhagic transformation on CT within the first 7 days.

Results—In nondiabetic patients, persistent hyperglycemia was inversely associated with neurological improvement (OR=0.31; 95% CI=0.16 to 0.60), 30-day favorable functional outcome (OR=0.27; 95% CI=0.12 to 0.62), and 90-day negligible dependence (OR=0.36; 95% CI=0.17 to 0.73); it was associated with an increased risk of mortality within 90 days (OR=7.61; 95% CI=3.23 to 17.90) and for parenchymal hemorrhage (OR=6.64; 95% CI=2.63 to 16.78), whereas it was inversely associated with hemorrhagic infarction (OR=0.30; 95% CI=0.13 to 0.71). Delayed hyperglycemia at 24 hours was associated with the risks of death (OR=5.99; 95% CI=2.51 to 14.2) and parenchymal hemorrhage (OR=5.69; 95% CI=2.05 to 15.8) and inversely associated with no and negligible dependency (OR=0.40; 95% CI=0.20 to 0.78). Hyperglycemia at baseline only was not associated with any parameter of worse outcome. In patients with diabetes, the dynamic patterns of hyperglycemia did not suggest an association with stroke outcome.

Conclusions—Persistent hyperglycemia was associated with all bad outcome end points studied. In addition to a single glucose measurement, the pattern of change should be considered in the prediction of stroke outcome. (Stroke. 2008;39:2749-2755.)

Key Words: hyperglycemia ■ ischemic stroke ■ outcome ■ prediction ■ recombinant tissue plasminogen activator ■ serum glucose

Hyperglycemia is prevalent in 20% to 50% of patients with acute ischemic stroke even without a disease history of diabetes mellitus. A number of clinical studies have revealed an association between acute hyperglycemia and increased mortality and poor functional outcome as summarized in a meta-analysis. The potential mechanisms of elevated blood glucose after cerebral ischemia include stress response, which would account for its correlation with stroke severity, or it is associated with abnormal carbohydrate metabolism in case of pre-existing diabetes mellitus or impaired glucose tolerance. Nondiabetic hyperglycemia has been demonstrated to be an independent predictor of stroke outcome.

Most of the previous studies have concentrated on the admission glucose level without consideration of later evolvement of blood glucose after the admission of the patient with stroke. The kinetics of glucose after hospital admission is therefore less well evaluated with the outcome of patients, because cerebral ischemia is often progressive throughout the first day. Measuring blood glucose more often would be useful to understand the association among blood glucose, the early dynamic stroke pathology, and the outcome of patients. With 2 measurements of glucose within the first 12 hours in nondiabetics, Christensen and Boysen found increasing levels of serum glucose to be correlated with severe stroke symptoms and an increased short-term mortality rate. Persisting higher glucose levels predicted infarct expansion and functional outcome in 25 patients.

Because elevated levels of serum glucose are detrimental to neurons, hyperglycemia is considered to compromise the
beneficial effect of reperfusion after recombinant tissue plasminogen activator (rtPA) treatment. A deleterious effect of hyperglycemia on the outcome of stroke in connection with reperfusion after administration of rtPA has been revealed. Increased risk of intracranial hemorrhage and negative impact on neurological improvement has been observed for high admission blood glucose level in the National Institute of Neurological Diseases and Stroke trial database and in clinical routine. No association between high serum glucose and increased risk of hemorrhagic transformation was found in the TOAST trial database.

In the present study, we studied the associations among the 4 patterns of serum glucose levels measured at baseline and at 24 hours and stroke outcome, evaluated as neurological improvement in 7 days, functional outcome in 30 days, disability after 90 days, mortality within 90 days, and occurrences of hemorrhagic transformations within 7 days, in the second European Cooperative Acute Stroke Study (ECASS-II) database. The following questions are addressed in the present study: (1) Do the dynamic patterns of hyperglycemia impact differently on stroke outcome? (2) Is a single baseline glucose level enough to make a prediction of the outcome?

Materials and Methods

Patient Population

The patient sample is from the ECASS-II, which was a multicenter, randomized, double-blind, placebo-controlled trial to test the efficacy and safety of rtPA in acute hemispheric stroke. Eight hundred eligible patients were randomly assigned to either 0.9 mg/kg rtPA or placebo. Seven patients did not receive trial medication. Intravenous administration of trial medication was started within 6 hours of the onset of symptoms. Among the 793 treated patients, 407 received rtPA and 386 placebo. Nine patients were lost to follow-up and all patients underwent the 90-day assessment.

Aims, methodology, and patient inclusion and exclusion criteria have been described previously in more detail. Patients who received sufficient heparin to elevate the activated partial thromboplastin time or warfarin to increase the international normalized ratio to a therapeutic level were excluded from the study. Administration of oral anticoagulants, antiplatelet agents, hemorheologic agents, and brain-protective drugs was not permitted during the initial 24 hours after the administration of the study drug. Patients with baseline blood glucose levels <2.75 mmol/L (50 mg/dL) or >22.0 mmol/L (400 mg/dL) were also excluded. Patients were considered diabetic only if their disease history revealed diabetes mellitus. Glucose management was not specified in the trial protocol and hence was only if their disease history revealed diabetes mellitus. Glucose (400 mg/dL) were also excluded. Patients were considered diabetic brain-protective drugs was not permitted during the initial 24 hours.

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Outcome

Five outcome measures were analyzed: 7-day neurological improvement assessed with the National Institutes of Health Stroke Scale (NIHSS), 30-day favorable functional outcome assessed with the Barthel Index, 90-day favorable outcome assessed with the modified Rankin Scale (mRS) score, death within 90 days after treatment, and hemorrhagic transformations within the first 7 days. Seven-day neurological improvement was defined as a 4-point decrease from baseline or zero points on the NIHSS at 7 days. Thirty-day Barthel Index of 95 or 100 was considered a favorable functional outcome. Ninety-day mRS was dichotomized into a favorable outcome (mRS 0, 1, or 2) or unfavorable outcome (mRS 3 to 6; death was graded 6). The fatal outcome was all-cause mortality within 90 days. Hemorrhagic transformations were distinguished according to ECASS-II criteria. Hemorrhagic infarction (HI) was defined as petechiae without a space-occupying effect, ranging from small petechiae along the margins of the infarct (HI1) to a confluent petechiae within the infarct area (HI2); parenchymal hemorrhage (PH) was defined as blood clots with space-occupying effect, either ≤30% (PH1) or >30% (PH2).

We categorized the timeline of neurofunctional recovery into the acute (within several days), subacute (within several weeks), and consolidation phases (lasting several months). Seven-day NIHSS change was used to examine the early neurological improvement. The cutoff (0 to 2 versus 3 to 6) of 90-day mRS was chosen as indicated in the primary report of ECASS-II. Intracranial hemorrhage events within 7 days (either intracranial hemorrhage at 24 to 36 hours or 7 days; overlapping is possible) were defined in accordance with the secondary analysis. We abandoned the outcome definition mRS + Barthel at 90 days in favor of mRS alone, because this has been better validated and is widely accepted.

Statistical Analysis

Data are presented as medians with interquartile ranges for continuous variables or frequencies for discrete variables as appropriate. χ² or Fisher exact tests were used for the categorical variables and 2-sided nonparametric Kruskal-Wallis test for the continuous variables in the univariate analyses. Multifactorial logistic regression models were used to assess the impact of hyperglycemia risk groups in reference to the normoglycemia group. Adjusted ORs were then obtained after the adjustment for the factors at a threshold probability value of 0.05 in the univariate analyses. These were age and gender of the patients, initial stroke severity assessed by NIHSS score, and disease history of hypertension and of congestive heart failure before stroke onset. Treatment with rtPA was included in the model because it was the test drug of the trial and its effect on outcome was implied. Data analyses were performed with the SAS Statistical Analysis System version 8.2 for AIX 4.3.2 operating system on a RS/6000 platform.

Results

Among the total 748 patients, who had completed admission and 24-hour glucose measurements, a slight decrease in median glucose level of 121 mg/dL (interquartile range: 104 to 149 mg/dL) at baseline and of 117 mg/dL (interquartile range: 101 to 146 mg/dL) at 24 hours was observed (P<0.0001 with paired comparison).

Patient Characteristics

Among the 161 patients with diabetes, 24 (15%) had a persistent normoglycemic level at baseline and at 24 hours, whereas 21 (13%) had elevated glucose only at baseline, 16 (10%) only at 24 hours, and 100 (62%) persistent hyperglycemia at baseline and at 24 hours. The distributions of demographic and clinical factors, disease and medication histories, and the CT signs of these 4 post hoc groups were compared; homogeneity in treatment assignment, time from onset to treatment, baseline body temperature and blood pressure, and CT findings are shown in Table 1. The persistent normoglycemic and the 24-hour hyperglycemic patients were more often male and had lower baseline systolic blood pressure.
Among the 587 nondiabetic patients, 408 (70%) had a persistent normoglycemic level at baseline and at 24 hours, whereas 79 (13.5%) had elevated glucose only at baseline, 54 (9%) only at 24 hours, and 46 (8%) persistent hyperglycemia at baseline and at 24 hours. The distributions of baseline characteristics of these groups were compared and are shown in Table 2. The patients with persistent normoglycemia were more often male and younger, had less severe neurological deficit, and less often had disease histories of hypertension and congestive heart failure.

Association of Hyperglycemic Patterns With Stroke Outcomes in Univariate Analyses

In the nondiabetic subcohort, when patients with baseline, 24-hour, and persistent hyperglycemia were compared with those with persistent normoglycemia, they had neurological improvement within the first 7 days (P=0.0022), 30-day favorable functional outcome defined as Barthel Index of 95 or 100 (P<0.0001), 90-day no or moderate residual disability defined as mRS 0 to 2 (P<0.0001), and significantly higher death rates within 90 days (P<0.0001) less often (Table 2). The patients with persistent hyperglycemia had parenchymal hemorrhages most often; the intergroup difference was statistically significant (P<0.0001). Hemorrhagic infarctions were observed more often in patients with baseline hyperglycemia (P=0.004).

In patients with diabetes, no association between the dynamic patterns of serum glucose and the stroke outcomes was observed (Table 3).

Association of Hyperglycemic Patterns With Stroke Outcomes in Multivariate Analyses

Among nondiabetic patients, patients with persistent hyperglycemia (Table 4) showed significantly decreased chance of have 7-day neurological improvement ≥4 points or 0 on NIHSS (OR=0.31, 95% CI=0.16 to 0.60) and to have 30-day favorable functional capacity defined as Barthel Index of 95 or 100 (OR=0.27, 95% CI=0.12 to 0.62) compared with patients with persistent normoglycemia after adjustment for the known baseline predictors. In relation to 90-day favorable outcome, defined as mRS 0 to 2, patients with 24-hour and persistent hyperglycemia were unfavorable (OR=0.40, 95% CI=0.20 to 0.78; OR=0.36, 95% CI=0.17 to 0.73, respectively) and had increased risk of death (OR=5.99, 95% CI=2.51 to 14.2; OR=7.61, 95% CI=3.23 to 17.90, respectively) compared with patients with normoglycemia. The patients with persistent hyperglycemic seemed to have the highest risk of parenchymal hemorrhage (OR=6.64, 95% CI=2.63 to 16.8) followed with 24-hour hyperglycemics only (OR=5.69, 95% CI=2.05 to 15.8), whereas the patients with persistent hyperglycemia had lowest risk to have a hemorrhagic infarction (OR=0.30, 95% CI=0.13 to 0.71).

In the nondiabetic subcohort, no significant association between the hyperglycemic patterns and stroke outcomes could be found.

Discussion

As far as we are aware, the present study is the first to investigate the dynamic patterns of hyperglycemia in associ-
Table 2. Baseline Characteristics of 587 Nondiabetic Patients According to the Hyperglycemic Patterns

| Baseline Characteristics | Baseline Hyperglycemia, n=79 (13.5%) | 24-Hour Hyperglycemia, n=54 (9.2%) | Persistent Hyperglycemia, n=46 (7.8%) | Persistent Normoglycemia, n=408 (69.5%) | P  
|--------------------------|------------------------------------------|----------------------------------|---------------------------------------|------------------------------------------|---
| rtPA, %                  | 41 (52%)                                 | 31 (57.4%)                       | 25 (54.4%)                            | 205 (50.3%)                             | 0.76  
| Male, %                  | 39 (49.4%)                               | 22 (40.7%)                       | 25 (54.4%)                            | 247 (60.5%)                             | 0.02  
| Age, years               | 70 (61–75)                               | 74 (66–76)                       | 72.5 (67–77)                          | 68 (57–73)                              | <0.0001  
| Onset of treatment interval, hours | 4.7 [3.7–5.3]                           | 4.7 [3.7–5.5]                   | 4.1 [3.1–5.5]                        | 4.2 [3.2–5.2]                           | 0.08  
| Baseline body temperature | 36.5 [36.2–36.8]                        | 36.5 [36.1–36.8]                | 36.6 [36.2–36.8]                     | 36.5 [36.1–36.9]                       | 0.72  
| Baseline diastolic blood pressure, mm Hg | 85 [80–92]                              | 85 [78–95]                      | 86 [80–94]                           | 86 [78–91]                             | 0.85  
| Extent of MCA hypodensity |                                        |                                 |                                       |                                         | 0.18  
| None, %                  | 33 (42%)                                 | 23 (43%)                        | 22 (48%)                             | 185 (45.5%)                             |  
| ≤33%, %                  | 44 (56%)                                 | 25 (46.3%)                      | 20 (43.5%)                           | 206 (50.6%)                             |  
| >33%, %                  | 2 (2.5%)                                 | 6 (11.1%)                       | 4 (8.7%)                             | 16 (3.9%)                              |  
| Hypertension history, %  | 46 (58.2%)                               | 36 (66.7%)                      | 28 (60.9%)                           | 172 (42.2%)                             | 0.0002  
| Congestive heart failure, % | 5 (6.3%)                              | 6 (11.1%)                       | 5 (11%)                             | 15 (3.7%)                              | 0.03  
| Coronary heart ischemia, % | 12 (15.2%)                              | 10 (18.5%)                      | 13 (28.3%)                           | 85 (20.8%)                             | 0.36  
| Transient ischemic attack, % | 3 (4%)                                  | 4 (7.4%)                        | 4 (8.7%)                             | 39 (9.6%)                              | 0.41  
| Atrial fibrillation, %   | 24 (30.4%)                               | 12 (22.2%)                      | 16 (34.8%)                           | 84 (20.6%)                             | 0.06  

Numbers in brackets are interquartile ranges.
Note: Discrete variables were tested with χ² or Fisher exact test, as appropriate; continuous variables with Kruskal-Wallis test; P values were not adjusted for multiple testing.
SSS indicates Scandinavian Stroke Scale; MCA, middle cerebral artery.

Table 3. Univariate Associations Between Hyperglycemic Patterns and Outcomes

| Outcome | Baseline Hyperglycemia | 24-Hour Hyperglycemia | Persistent Hyperglycemia | Persistent Normoglycemia | P*  
|---------|-------------------------|-----------------------|--------------------------|--------------------------|---
| Diabetics, N=161 | 21 (13%) | 16 (10%) | 100 (62%) | 24 (15%) | 0.47  
| 7-day neurological improvement ≥4 or 0 points on NIHSS | 6 (28.6%) | 8 (50%) | 43 (43%) | 12 (50%) |  
| 30-day Barthel Index 95, 100 | 3 (14.3%) | 3 (18.8%) | 33 (33%) | 8 (33.3%) | 0.29  
| 90-day mRS 0, 1, or 2 | 4 (19.1%) | 5 (31.3%) | 42 (42%) | 12 (50%) | 0.14  
| 90-day death | 4 (19.1%) | 2 (12.5%) | 9 (9%) | 2 (8.3%) | 0.49  
| HI within 7 days | 6 (28.6%) | 5 (31.3%) | 36 (36%) | 9 (37.5%) | 0.92  
| PH within 7 days | 3 (14.3%) | 1 (6.3%) | 6 (6%) | 1 (4.2%) | 0.52  
| Nondiabetics, N=587 | 79 (13%) | 54 (9%) | 46 (8%) | 408 (70%) |  
| 7-day neurological improvement ≥4 or 0 points on NIHSS | 44 (55.7%) | 27 (50%) | 15 (32.6%) | 248 (60.8%) | 0.0022  
| 30-day Barthel Index 95, 100 | 32 (40.5%) | 18 (33.3%) | 9 (19.6%) | 196 (48.0%) | 0.0001  
| 90-day mRS 0, 1, or 2 | 43 (54.4%) | 19 (35.2%) | 15 (32.6%) | 241 (59.1%) | 0.0001  
| 90-day death | 8 (10.1%) | 14 (25.9%) | 14 (30.4%) | 20 (4.9%) | 0.0001  
| HI within 7 days | 39 (49.4%) | 19 (35.2%) | 8 (17.4%) | 146 (35.8%) | 0.004  
| PH within 7 days | 5 (6.3%) | 9 (16.7%) | 10 (21.7%) | 17 (4.2%) | 0.0001  

*With Fisher exact test.
subgroup of patients with acute and transient hyperglycemia at baseline did not have an increased risk of worse outcome in any of the outcome parameters of the present study. This finding made us doubt a systematic overestimation of baseline hyperglycemia in previous studies.

One of the potential explanations of the detrimental effect of hyperglycemia is the comorbidity caused by diabetes mellitus, which is responsible for elevated glucose and poorer prognosis. The prognosis from stroke associated with diabetes mellitus may be attributed to such factors as diabetes-induced neuropathy and formation and accumulation of lactate production or a variety of secondary mechanisms, including anaerobic metabolism in hyperglycemic condition. In the present study, 21% of patients with baseline hyperglycemia as well as 23% of patients with delayed hyperglycemia were diabetic, whereas 68.5% of patients with persistent hyperglycemia. It is plausible that patients with diabetic stroke have different dynamic patterns of hyperglycemia compared with nondiabetic patients with stroke. Hence, separate analyses in diabetics and nondiabetics were carried out. We could not reveal any association between dynamic patterns of serum glucose and stroke outcome in diabetics, whereas the nondiabetic patients with persistent hyperglycemia had the worst outcome.

Stress response has been thought to be an explanation of poststroke hyperglycemia that may adversely affect stroke outcome. Capes et al have reported a 3-fold increased risk on mortality in poststroke hyperglycemia, summarizing 9 studies in nondiabetic patients. The so-called reactive hyperglycemia can be attributed to activation of the hypothalamic–pituitary–adrenal axis. Several studies have reported a correlation between glucose level and neurological stroke severity or infarct size, which are also associated with poorer prognosis. However, Toni and coworkers could not confirm this observation. In the present study, the weak correlation between the baseline glucose level and NIHSS score \((r=0.10, P=0.004)\) and that between the decrease of glucose level and neurological improvement during the first 24 hours after admission \((r=0.08, P=0.02)\) do not convincingly verify that hyperglycemia is caused by the severity of stroke. Van Kooten et al have concluded that hyperglycemia in the acute phase of stroke cannot be attributed to stress. The assumption that the extent of an injury and the outcome of patients do not depend on a momentary level of serum glucose but a more sustained state of hyperglycemia seems more appropriate. The observation by Baird that the higher mean glucose over time but not the baseline glucose enlarged the infarct volume also supports our results of the importance of dynamics of hyperglycemia. In our study, the effect of dynamic patterns of hyperglycemia on the outcome was adjusted for stroke severity. Patients with persistent hyperglycemia had less often hemorrhagic infarction but more often parenchymal hemorrhage. Some study findings suggested that HI may not be benign and even be a marker of reperfusion, whereas PH is an adverse event resulted from tPA and other factors. A distinction in terms of different pathogenesis of HI and PH is supported again in a recent work.

In the ECASS-II database, a decrease in blood glucose from baseline to 24 hours has been observed both in diabetic and nondiabetic patients. It is in agreement with the findings of Gray and coworkers that the mean plasma glucose level declines within 24 hours without specific intervention. On the contrary, an increase within 12 hours has been observed in patients without a history of diabetes mellitus. Comparing the results with other trials, in the ECASS-II database, patients with baseline and transient hyperglycemia seem to be at lower risk of an unfavorable outcome. The recent randomized, controlled trial to intervene in the glucose level
could not reveal a beneficial effect to reduce mortality at 90 days or secondary outcome despite the successful decline in the glucose level. However, the mean time from stroke onset to treatment was delayed to approximately 12 hours in this trial. A future investigation is needed to reassess the efficacy with an earlier intervention.

The present study has several advantages. First, the baseline glucose was measured within 6 hours after stroke onset according to the trial protocol of ECASS instead of late measurements in many other trials. The assessment of whether the admission glucose level results in poor outcome may therefore be less biased. Another advantage of the present study is that the repeated measurement at 24 hours after the admission made it possible to assess the dynamic of serum glucose on the outcome rather than baseline glucose. Few studies have considered the serial measurements of blood glucose. Baird et al. used continuous glucose monitoring, which in a large clinical trial may not be feasible. The novelty of the present study is that the patients were categorized according to the dynamic patterns of their glucose, and the impact of the pattern of glucose on the outcome was assessed instead of using only baseline glucose as the prediction model.

The present study treated ECASS-II data, in which the patients were not randomly assigned according to the glucose level, as an observational study, and hence has limitations attributable to its post hoc nature. The heterogeneities between the hyperglycemic groups are present. Even after the adjustment for known confounders, residual confounding from unobserved factors has to be considered. Patients who had minor stroke symptoms and who showed rapid improvement of the symptoms at the time of randomization were excluded from ECASS-II; hence, the study population may not be representative of nonselected patients with stroke. Exclusion of patients with very high hyperglycemia (>400 mg/dL) might result in an underestimation of risk. Forty-five patients, of which 7 did not have the baseline measurement and 38 did not have the 24-hour measurement, were excluded from the analyses because their dynamic pattern could not be determined. Missing values were not replaced by means of imputation technique, which would create again mathematical artifacts. Instead, the comparability in terms of the baseline structural homogeneity between these 45 excluded patients with the included 748 patients was checked. Except for the fact that the 45 patients were significantly younger than the others, no other structural difference was detected.

Seven patients died within 24 hours, of which 4 were baseline hyperglycemic. Underestimation of the risk of poor outcome of nondiabetic patients with hyperglycemia on admission or at 24 hours is possible. Furthermore, the patients with unknown diabetes or glucose intolerance could not be considered because of lack of information, which may cause the additional bias. Despite standardized protocol, variation in glucose measurement among the 108 centers has to be considered. Because the present study evaluates the dynamic pattern according to the intraindividual measurements, measurement error within patients should be minimal. Two measurements of glucose concentration in the acute phase were available in the present study. More frequent measurements would have been desirable so we could have analyzed the dynamics of hyperglycemia more accurately including the duration of hyperglycemia and its impact on the outcome.

In conclusion, our present analysis suggests that the dynamic patterns of hyperglycemia contribute to prognosis of stroke outcome. Nondiabetic patients with persistent hyperglycemia had the worst prognosis assessed by neurological improvement, functional outcome, mortality, and hemorrhagic transformation. This suggests that hyperglycemia in nondiabetic patients with stroke should be treated. Patients with delayed hyperglycemia implied increased risk of long-term dependency, mortality, and 7-day parenchymal hemorrhage, which also suggests that hyperglycemia needs to be treated. This underlines the importance of glucose monitoring and the treatment of hyperglycemia in the early phase. The dynamics of glucose and the duration of hyperglycemia should be studied in more detail in future studies.

Disclosures

None.

References


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