Original Article

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Transient hyperglycemia at admission and acute ischemic stroke severity and short-term outcome

K. Tziomalos*, P. Dimitriou, S. D. Bouziana, M. Spanou, S. Kostaki, S. Angelopoulou, M. Papadopoulou, V. Giampatzis, C. Savopoulos, A. I. Hatzitolios

First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, "AHEPA" Hospital, Thessaloniki, Greece

Abstract

Stress hyperglycemia is frequent during acute ischemic stroke. However, it is unclear whether it only reflects stroke severity or if it directly contributes to adverse outcome. To address this question, we prospectively studied 790 consecutive patients with acute ischemic stroke. Stress hyperglycemia was defined as fasting serum glucose levels at the second day after admission ≥126 mg/dl in non-diabetic patients. Patients with stress hyperglycemia had more severe stroke. However, stress hyperglycemia did not predict adverse outcome at discharge or in-hospital mortality in multivariate analyses adjusting for stroke severity. In conclusion, stress hyperglycemia does not appear to directly affect the outcome of acute ischemic stroke.

Key words: ischemic stroke; outcome; stress hyperglycemia; type 2 diabetes mellitus

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Introduction

Ischemic stroke is a leading cause of death and long-term disability worldwide.[1,2] The presence of type 2 diabetes mellitus (T2DM) more than doubles the risk of ischemic stroke.[3,4] Furthermore, ischemic stroke is more severe in patients with T2DM and is also associated with poorer functional outcomes and higher risk of death.[5-7] Moreover, preliminary data suggest that antidiabetic treatment might ameliorate stroke severity and improve the outcome of acute ischemic stroke.[8-11]

***Corresponding author: Konstantinos Tziomalos**, MD, Phd, 1st Propedeutic Department of Internal Medicine, "AHEPA" Hospital, 1 Stilponos Kyriakidi street, GR-546 36, Thessaloniki, Greece
Tel.: (+30) 2310-994621, Fax: (+30) 2310-994773, E-mail: ktziomalos@yahoo.com

In contrast with the established adverse effects of T2DM on stroke severity and outcome, it is unclear whether acute elevations in glucose levels during acute ischemic stroke adversely affect the outcome of non-diabetic patients. During acute ischemic stroke, stress stimulates the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system leading to release of stress hormones, including cortisol and catecholamines, which increase glucose levels.[4] This phenomenon, coined stress hyperglycemia, is present in approximately 8-35% of non-diabetic patients with acute ischemic stroke.[4,12,13] Several studies reported worse outcomes in patients with acute ischemic stroke who exhibit stress hyperglycemia.[13-15] However, stress hyperglycemia is more frequent in patients with more severe stroke.[16-19] Therefore, it is unclear whether this association between stress hyperglycemia and stroke outcome is causal or is due to a greater stroke severity in patients with stress hyperglycemia. Moreover, many studies did not differentiate between patients with stress hyperglycemia and those with established T2DM.[20-23]

The aim of the present study was to evaluate whether stress hyperglycemia is associated with the functional outcome at discharge and the in-hospital mortality of non-diabetic patients with acute ischemic stroke.

Patients and methods

We prospectively studied all patients who were admitted in our Department with acute ischemic stroke between September 2010 and March 2015 (n= 790; 41.0% males, age 79.4±6.8 years).

At admission, demographic data (age, sex), history of cardiovascular risk factors [hypertension, T2DM, atrial fibrillation (AF), smoking, alcohol consumption, family history of cardiovascular disease (CVD)], history of concomitant CVD (coronary heart disease (CHD), previous ischemic stroke, heart failure) and pharmacological treatment were recorded. Anthropometric parameters (weight, height, waist and hip circumference) and systolic and diastolic blood pressure were also measured. The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS).

Routine laboratory investigations were performed after overnight fasting at the first day after admission and included serum levels of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine and uric acid. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald's formula.[24] Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[25] Chronic kidney disease was defined as estimated GFR (eGFR) < 60 ml/min/1.73m^2.

Type 2 diabetes mellitus was defined as a history of physician-diagnosed T2DM or treatment with antidiabetic agents. Stress hyperglycemia was defined as fasting serum glucose levels at the first day after admission ≥ 126 mg/dl in patients without T2DM.

All patients underwent brain computed tomography at admission and a second brain computed tomography was performed if clinically indicated.

The outcome was assessed with adverse outcome rates at discharge and with in-hospital mortality. Adverse outcome was defined as a modified Rankin scale at discharge between 2 and 6.

Statistical analysis

All data were analyzed with the statistical package SPSS (version 17.0; SPSS, Chicago, IL, USA). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Serum TG levels were log-transformed to normalize their distribution. Differences in categorical variables between groups were assessed with the chi-square test. Differences in continuous variables between groups were assessed with one-way analysis of variance and pair-wise post-hoc comparisons between groups were performed with the Holm-Sidak test. Binary logistic regression analysis was used to identify independent predictors of adverse outcome at discharge and in-hospital mortality. In all cases, a two-tailed $p < 0.05$ was considered significant.

Results

At admission, 32.0% of the total study population had T2DM. At the second day after admission, 8.6%

Table 1. **Characteristics of patients with stress hyperglycemia, type 2 diabetes mellitus (T2DM) and neither stress hyperglycemia nor T2DM ("normoglycemia")**

	Patients with stress hyperglycemia (n = 68)	Patients with T2DM (n = 253)	Patients with normoglycemia (n = 469)	p (overall)	p (for pair-wise comparisons)		
					Stress hyperglycemia vs. T2DM	Stress hyperglycemia vs. normoglycemia	T2DM vs. normoglycemia
Age (years)	81.5±6.5	78.7±6.3	79.5±7.1	<0.05	<0.05	NS	NS
Males (%)	39.7	41.1	41.2	NS	NS	NS	NS
SBP (mmHg)	150±29	151±26	148±25	NS	NS	NS	NS
DBP (mmHg)	84±15	81±13	80±15	NS	NS	NS	NS
Heart rate	84±18	79±14	77±15	<0.005	NS	<0.005	NS
Hypertension (%)	79.4	83.8	80.2	NS	NS	NS	NS
Smoking (current/past, %)	5.9/11.8	13.8/18.2	13.4/17.7	NS	NS	NS	NS
Package-years	72±44	68±53	67±52	NS	NS	NS	NS
Atrial fibrillation (%)	48.5	34.8	32.2	<0.05	NS	<0.05	NS
Alcohol (units/week)	3.7±23.2	0.7±2.2	1.3±6.0	<0.05	<0.05	NS	NS
BMI (kg/m^2)	27.1±4.0	28.3±5.4	26.8±4.8	<0.01	NS	NS	<0.01
Waist (cm)	101±13	109±11	103±13	<0.005	NS	NS	<0.005
Waist/hip	0.99±0.09	0.99±0.06	0.97±0.07	NS	NS	NS	NS
Overweight/obese (%)	51.5/19.1	39.9/30.8	41.4/21.1	NS	NS	NS	NS
Family history of CVD (%)	17.6	16.6	14.7	NS	NS	NS	NS
CHD (%)	22.1	32.8	24.1	<0.05	NS	NS	<0.05
Prior ischemic stroke (%)	44.1	46.6	42.4	NS	NS	NS	NS
CKD (%)	44.1	36.7	31.8	NS	NS	NS	NS
Heart failure (%)	19.1	21.3	12.2	<0.005	NS	NS	<0.005
Glucose (mg/dl)	156±28	148±67	93±15	<0.001	NS	<0.001	<0.001
LDL-C (mg/dl)	111±49	101±40	112±37	<0.001	NS	NS	<0.001
HDL-C (mg/dl)	50±18	43±14	48±14	<0.001	<0.007	NS	<0.001
Triglycerides (mg/dl)	121±79	135±69	108±47	<0.001	NS	NS	<0.001
Uric acid (mg/dl)	6.2±2.3	5.8±1.8	5.7±1.9	NS	NS	NS	NS
eGFR (ml/min/1.73m^2)	64±24	70±25	71±24	NS	NS	NS	NS
NIHSS	15.9±10.5	8.6±8.7	7.7±8.4	<0.001	<0.001	<0.001	NS

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; CVD: cardiovascular disease; CHD: coronary heart disease; CKD: chronic kidney disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; NIHSS: National Institutes of Health Stroke Scale.

Table 2. Significant differences between patients with adverse outcome and those with favorable outcome

	Patients with adverse outcome (n = 508)	Patients with favorable outcome (n = 282)	p
Age (years)	80.6±6.9	77.3±6.2	<0.001
Heart rate	80±16	76±13	<0.001
Atrial fibrillation (%)	39.0	27.0	<0.001
Prior ischemic stroke (%)	49.2	36.3	<0.001
Glycemic status (%)			
Stress hyperglycemia	11.5	4.6	<0.005
Type 2 diabetes mellitus (T2DM)	33.0	30.9	
Neither stress hyperglycemia nor T2DM	55.5	64.5	
Total cholesterol (mg/dl)	176±45	184±45	<0.05
Triglycerides (mg/dl)	114±62	123±53	<0.005*
Glomerular filtration rate (ml/min/1.73m^2)	68±25	73±24	<0.05
National Institutes of Health Stroke Scale	12.0±9.3	2.2±2.6	<0.001

*for the comparison of log-transformed triglyceride levels

of the total study population had stress hyperglycemia (i.e. 12.7% of the non-diabetic patients). Characteristics of patients with stress hyperglycemia, T2DM and neither stress hyperglycemia nor T2DM are shown in **Table 1**. Patients with stress hyperglycemia were older than patients with T2DM and had higher HDL-C levels and more severe stroke. Patients with stress hyperglycemia also had higher prevalence of AF, higher heart rate and more severe stroke than patients with neither stress hyperglycemia nor T2DM. On the other hand, patients with T2DM had higher body mass index and waist circumference, higher prevalence of CHD and heart failure, lower LDL-C and HDL-C levels and higher TG levels but similar stroke severity compared with patients with neither stress hyperglycemia nor T2DM.

At discharge, 64.3% of patients had adverse outcome. Patients with stress hyperglycemia had higher rate of adverse outcome than patients with T2DM and patients with neither stress hyperglycemia nor T2DM (80.9, 65.6 and 60.8%, respectively; p < 0.005). Other significant differences between patients with adverse outcome at discharge and those with favorable outcome are shown in **Table 2**. The former were older than those who had favorable outcome (p<0.001) and had higher prevalence of AF and prior ischemic stroke (p<0.001 for both comparisons), higher heart rate (p<0.05), lower serum TC and log-TG levels (p<0.05 and p<0.005, respectively), lower eGFR (p<0.05) and higher NIHSS at admission (p<0.001). In binary logistic regression analysis, independent predictors of adverse outcome at discharge were age (relative risk (RR) 1.08, 95% confidence interval (CI) 1.04-1.12, p<0.001), history of ischemic stroke (RR 1.68, 95% CI 1.05-2.69, p<0.05) and NIHSS at admission (RR 1.50, 95% CI 1.38-1.63, p<0.001). When the NIHSS at admission was removed from the multivariate model, independent predictors of adverse outcome at discharge were age (RR 1.08, 95% CI 1.05-1.11, p<0.001), history of ischemic stroke (RR 1.68, 95% CI 1.18-2.39, p<0.005), log-TG levels (RR 0.33, 95% CI 0.12-0.89, p<0.05) and

Table 3. Significant differences between patients who died during hospitalization and those who were discharged

	Patients who died during hospitalization (n = 73)	Patients who were discharged (n = 717)	p
Age (years)	82.7±7.2	79.0±6.7	<0.001
Diastolic blood pressure (mmHg)	88±19	80±13	<0.001
Heart rate	84±17	78±15	<0.001
Atrial fibrillation (%)	65.8	31.2	<0.001
Glycemic status (%) Stress hyperglycemia Type 2 diabetes mellitus (T2DM) Neither stress hyperglycemia nor T2DM	 28.8 31.5 39.7	 6.5 32.1 61.4	 <0.001
Triglycerides (mg/dl)	99±43	120±60	<0.001*
National Institutes of Health Stroke Scale	23.8±9.1	7.1±7.3	<0.001

*for the comparison of log-transformed triglyceride levels

stress hyperglycemia (patients with stress hyperglycemia vs. patients with neither stress hyperglycemia nor T2DM: RR 2.39, 95% CI 1.16-4.93, p<0.05; patients with T2DM *vs* patients with neither stress hyperglycemia nor T2DM: RR 1.26, 95% CI 0.85-1.85, p = NS).

During hospitalization, 9.2% of patients died. Patients with stress hyperglycemia had higher in-hospital mortality rate than patients with T2DM and patients with neither stress hyperglycemia nor T2DM (30.9, 9.1 and 6.2%, respectively; p<0.001). Other significant differences between patients who died during hospitalization and those who were discharged are shown in **Table 3**. The former were older than patients who were discharged (p<0.001) and had higher prevalence of AF (p< 0.001), higher diastolic blood pressure (p<0.001), higher heart rate (p<0.001), lower serum log-TG levels (p<0.005) and higher NIHSS at admission (p<0.001). In binary logistic regression analysis, independent predictors of in-hospital mortality were AF (RR 2.49, 95% CI 1.19-5.21, p<0.05), diastolic blood pressure (RR 1.05, 95% CI 1.03-1.08, p<0.001), serum log-TG levels (RR 0.10, 95% CI 0.01-0.80, p<0.05) and NIHSS at admission (RR 1.19, 95% CI 1.14-1.24, p<0.001). When the NIHSS at admission was removed from the multivariate model, independent predictors of in-hospital mortality were age (RR 1.08, 95% CI 1.03-1.14, p<0.005), AF (RR 2.97, 95% CI 1.60-5.49, p<0.001), diastolic blood pressure (RR 1.04, 95% CI 1.02-1.06, p<0.001), serum log-TG levels (RR 0.09, 95% CI 0.02-0.52, p<0.01) and stress hyperglycemia (patients with stress hyperglycemia *vs* patients with neither stress hyperglycemia nor T2DM: RR 5.50, 95% CI 2.51-12.05, p<0.001; patients with T2DM *vs* patients with neither stress hyperglycemia nor T2DM: RR 1.91, 95% CI 0.95-3.85, p = NS).

Discussion

The main finding of the present study is that stress hyperglycemia during acute ischemic stroke in non-diabetic patients does not directly increase the risk of adverse outcome. Indeed, the association between stress hyperglycemia and adverse functional outcome and increased in-hospital mortality appears to be due to the greater stroke severity in patients with stress hyperglycemia.

Patients with stress hyperglycemia had more severe stroke at admission than patients with T2DM and patients with neither stress hyperglycemia nor

T2DM. These findings are in agreement with 2 previous small studies.[14,26] Others also reported that more severe stroke is associated with stress hyperglycemia in non-diabetic patients.[16-19] The size of infarct also correlates with serum glucose levels at admission.[14,27] These associations are probably due to the more pronounced stress response in patients with more severe stroke.[4,28] Indeed, cortisol levels are the main determinant of glucose levels during acute stroke.[28]

In the present study, patients with stress hyperglycemia had worse functional outcome than both patients with T2DM and patients with neither stress hyperglycemia nor T2DM. However, in multivariate analysis, stress hyperglycemia was not an independent predictor of adverse outcome. When stroke severity was removed from the multivariate model, stress hyperglycemia was associated with higher risk for adverse outcome, suggesting that the relationship between stress hyperglycemia and outcome is due to the more severe stroke in these patients. Indeed, in patients with acute stroke, cortisol, but not glucose levels, predicted the outcome, further supporting the notion that glucose is a marker of stress response and not a direct cause of adverse outcome.[28] Notably, an early meta-analysis reported that non-diabetic patients with stress hyperglycemia had higher risk for poor functional recovery up to 6 months after stroke.[13] However, only unadjusted associations between stress hyperglycemia and functional outcome were reported and stroke severity was not considered in the analyses.[13] Other studies reported worse functional outcome at 30 days in patients with hyperglycemia at admission but did not differentiate between patients with stress hyperglycemia and patients with T2DM.[20-23] On the other hand, a post-hoc analysis of the second European Cooperative Acute Stroke Study (ECASS-II) showed that non-diabetic patients with serum glucose levels >140 mg/dl at 24h after admission for acute ischemic stroke have worse functional outcome at 90 days independently of stroke severity at admission.[29] However, these findings have the inherent limitations of a post-hoc analysis; moreover, patients with minor strokes were excluded from ECASS-II, limiting the generalizability of these results.[29]

Patients with stress hyperglycemia had higher in-hospital mortality rates than patients with T2DM and patients with neither stress hyperglycemia nor T2DM. However, these differences did not persist in multivariate analysis adjusting for stroke severity, again suggesting that stress hyperglycemia does not directly contribute to the outcome of acute ischemic stroke. Previous studies reported higher in-hospital mortality in non-diabetic patients with ischemic stroke and stress hyperglycemia but did not adjust for differences in stroke severity.[13-15] In studies with longer follow-up, stress hyperglycemia did not predict mortality at 1 year in non-diabetic patients when stroke severity was included in multivariate analyses.[26] In contrast, a retrospective study (n= 447) reported higher mortality at 90 days in non-diabetic patients with non-fasting glucose levels >130 mg/dl at admission, independently of stroke severity.[18] However, stroke severity was evaluated retrospectively in this study on the basis of the neurological evaluation performed at admission.[18] The afore-mentioned post-hoc analysis of the ECASS-II also reported higher mortality at 90 days in patients with serum glucose levels >140 mg/dl at 24h after admission, independently of stroke severity, but the same limitations of a post-hoc analysis apply to these findings.[29]

In conclusion, stress hyperglycemia is associated with more severe acute ischemic stroke. Patients with stress hyperglycemia have more adverse functional outcome at discharge and higher in-hospital mortality but this association does not persist after adjustment for stroke severity. Therefore, stress hyperglycemia appears to reflect stroke severity and does not represent a direct cause of more adverse outcome. Indeed, tight glycemic control with insulin did not improve the functional outcome and did not reduce the mortality of patients with acute ischemic stroke but increased the risk of hypoglycemia.[30] Accordingly, stress hyperglycemia might be useful as an index of stroke severity but it is doubtful whether glucose-lowering treatments will improve the outcome of patients with acute ischemic stroke.

Conflict of interest:

All authors declare no conflict of interest.

Περίληψη

Παροδική υπεργλυκαιμία κατά την εισαγωγή και βαρύτητα και βραχυχρόνια έκβαση του οξέος ισχαιμικού αγγειακού εγκεφαλικού επεισοδίου

Κ. Τζιόμαλος, Π. Δημητρίου, Σ. Δ. Μπουζιανά, Μ. Σπανού, Σ. Κωστάκη, Σ. Αγγελοπούλου, Μ. Παπαδοπούλου, Β. Γιάμπατζης, Χ, Σαββόπουλος, Α. Ι. Χατζητόλιος

Α' Προπαιδευτική Παθολογική Κλινική, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο «ΑΧΕΠΑ», Θεσσαλονίκη, Ελλάδα

Η παροδική υπεργλυκαιμία είναι συχνή κατά τη διάρκεια της οξείας φάσης του ισχαιμικού αγγειακού εγκεφαλικού επεισοδίου (ΑΕΕ). Δεν είναι όμως σαφές αν η παροδική υπεργλυκαιμία αντανακλά μόνο τη βαρύτητα του ΑΕΕ ή αν επιπλέον συμβάλλει ανεξάρτητα στη δυσμενή έκβαση αυτών των ασθενών. Για να απαντηθεί αυτό το ερώτημα, μελετήσαμε προοπτικά 790 διαδοχικούς ασθενείς με οξύ ισχαιμικό ΑΕΕ. Ως παροδική υπεργλυκαιμία ορίστηκε επίπεδα γλυκόζης ορού νηστείας τη 2η μέρα της νοσηλείας ≥126 mg/dl σε μη διαβητικούς ασθενείς. Οι ασθενείς με παροδική υπεργλυκαιμία είχαν βαρύτερο ΑΕΕ. Εντούτοις, η παροδική υπεργλυκαιμία δεν προέβλεπε τη δυσμενή λειτουργική έκβαση κατά την έξοδο από το νοσοκομείο ή την ενδονοσοκομειακή θνητότητα σε πολυπαραγοντική ανάλυση, μετά από στάθμιση για τη βαρύτητα του ΑΕΕ. Συμπερασματικά, η παροδική υπεργλυκαιμία δε φαίνεται να επηρεάζει άμεσα την έκβαση του οξέος ισχαιμικού ΑΕΕ.

Λέξεις ευρετηρίου: αγγειακό εγκεφαλικό επεισόδιο, έκβαση, ισχαιμικό, παροδική υπεργλυκαιμία, σακχαρώδης διαβήτης τύπου 2

***Στοιχεία υπεύθυνου συγγραφέα: Κωνσταντίνος Τζόμαλος**, MD, Phd, Α' Προπαιδευτική Παθολογική Κλινική, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο «ΑΧΕΠΑ», Στίλπωνος Κυριακίδη 1, 546 36, Θεσσαλονίκη, Ελλάδα
Τηλ.: 2310-994621, Fax: 2310-994773, E-mail: ktziomalos@yahoo.com

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