

Hyperglycemia and diabetes have different impacts on outcome of ischemic and hemorrhagic stroke

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Abstract

Introduction: Stroke is the second leading cause of long-term disability and death worldwide. Diabetes and hyperglycemia may impact the outcome of stroke. We examined the impact of hyperglycemia and diabetes on in-hospital death among ischemic and hemorrhagic stroke patients.

Material and methods: Data from 766 consecutive patients with ischemic (83.15%) and hemorrhagic stroke were analyzed. Patients were classified into four groups: ischemic and diabetic; ischemic and non-diabetic; hemorrhagic and diabetic; and hemorrhagic and non-diabetic. Serum glucose was measured on admission at the emergency department together with biochemical and clinical parameters.

Results: Mean admission glucose in ischemic stroke patients with diabetes was higher than in non-diabetic ones ($p < 0.001$) and in hemorrhagic stroke patients with diabetes than in those without diabetes ($p < 0.05$). Mean admission glucose in all patients who died was significantly higher than in patients who survived. In multivariate analysis, the risk factors for outcome in patients with ischemic stroke and without diabetes were age, admission glucose level and estimated glomerular filtration rate (eGFR), while in diabetics they were female gender, admission glucose level, and eGFR; in patients with hemorrhagic stroke and without diabetes they were age and admission glucose levels. The cut-off value in predicting death in patients with ischemic stroke and without diabetes was above 113.5 mg/dl, while in diabetics it was above 210.5 mg/dl.

Conclusions: Hyperglycemia on admission is associated with worsened clinical outcome and increased risk of in-hospital death in ischemic and hemorrhagic stroke patients. Diabetes increased the risk of in-hospital death in hemorrhagic stroke patients, but not in ischemic ones.

Key words: stroke, diabetes, outcome, mortality, hyperglycaemia.

Introduction

Stroke is the second leading cause of long-term disability and is the second leading cause of death worldwide. The incidence of stroke can be reduced by elimination of risk factors in the healthy population (such as smoking, obesity, inactivity, unhealthy diets, and excessive alcohol intake) and by treatment of known risk factors for stroke (hypertension, diabetes, heart disease, lipid and coagulation disorders, inflammation).

Diabetes prevalence is estimated between 15% and 25% of patients with ischemic stroke [1–4], but undiagnosed diabetes and impaired glucose tolerance account for 5–28% [5]. Diabetes is associated with an increased risk of ischemic stroke, and it also changes its clinical picture and affects the outcome [6]. Hyperglycemia is common during the acute period of stroke and can occur in patients with or without diabetes [3, 7]. Hyperglycemia is an independent risk factor for poor clinical outcome [3, 5, 8–11]. Hyperglycemia occurs in 30–40% of patients with acute ischemic stroke [5, 12, 13] and 43–59% of hemorrhagic stroke patients [14]. According to the literature, there is a lack of clear data that diabetes is a risk of in-hospital death.

The aim of this study was to investigate the impact of hyperglycemia and diabetes on in-hospital death amongst ischemic and hemorrhagic stroke patients. Furthermore, we evaluated selected risk factors affecting hospital events, in-hospital outcome and the length of hospitalization of patients with ischemic and hemorrhagic stroke.

Material and methods

We analyzed 766 consecutive patients with ischemic and hemorrhagic stroke who were admitted to the Department of Neurology, Medical University Hospital (Bialystok, Poland). Stroke was diagnosed based on neurological examination and admission computed tomography scan. Patients with subarachnoid hemorrhage, transient ischemic attacks, after loss of consciousness, brain tumor, head trauma and patients with incomplete data were excluded. No patient underwent thrombolysis. Patients were classified into four groups: patients with ischemic stroke and diabetes, patients with ischemic stroke and without diabetes, patients with hemorrhagic stroke and diabetes, and patients with hemorrhagic stroke and without diabetes.

Clinical variables

At admission demographic data (age, gender), metabolic parameters (serum glucose, creatinine, cholesterol) were recorded. At admission venous plasma glucose level was measured in the emergency room. All patients underwent brain computed tomography at admission. Hypertension, coronary heart disease, history of myocardial infarction, atrial fibrillation, and history of previous stroke were recorded. Diabetes was defined if the patient had a history of diabetes that was confirmed by their medical records or was using oral hypoglycemic treatment or insulin. The length of hospitalization was also recorded.

The study protocol was approved by the local Medical University Ethics Committee. All patients were fully informed about the study and gave their consent.

Results

We collected data from 766 patients with stroke (83.15% with ischemic and 16.84% with hemorrhagic stroke). The mean age of the study population was 70.90 ± 12.52 years. Patients with ischemic stroke were significantly older compared to hemorrhagic stroke patients (72.14 ± 11.38 ; 64.80 ± 15.76 years respectively; $p < 0.001$). The mean age of patients with ischemic stroke with and without diabetes was similar. The mean age of patients with hemorrhagic stroke and diabetes was 73.17 (non-significant – NS), and without diabetes 63.9 ($p = 0.054$) (Table I). Previous diagnosis of diabetes was established in 21.5% of patients with ischemic and 9.3% with hemorrhagic stroke ($p = 0.001$). A total of 668 (87.3%) patients had hypertension, comparable in both types of stroke (87.6% vs. 86.0%; NS). Hypertension occurred more frequently in patients with ischemic stroke and diabetes, compared to patients without dia-

Table I. Basal clinical characteristics of the studied population in relation to age and gender

| Parameter | Non-diabetic | | Diabetic | | Total | | P-value | |
|--------------------|--------------|-------------------|----------|-------------------|-------|-------------------|---------|-------|
| | N | Mean \pm SD/% | N | Mean \pm SD/% | N | Mean \pm SD/% | | |
| Age: | | | | | | | | |
| Hemorrhagic stroke | 499 | 71.92 \pm 11.90 | 137 | 72.90 \pm 9.28 | 636 | 72.13 \pm 11.38 | NS | |
| Ischemic stroke | 117 | 63.94 \pm 16.01 | 12 | 73.17 \pm 10.19 | 129 | 64.80 \pm 15.76 | 0.054 | |
| Gender: | | | | | | | | |
| Ischemic stroke | Males | 264 | 52.9 | 68 | 49.6 | 332 | 52.2 | 0.501 |
| | Females | 235 | 47.1 | 69 | 50.4 | 304 | 47.8 | |
| Hemorrhagic stroke | Males | 53 | 45.3 | 7 | 58.3 | 60 | 46.5 | 0.545 |
| | Females | 64 | 54.7 | 5 | 41.7 | 69 | 53.5 | |

betes (86.1 vs. 92.7%, respectively $p = 0.041$). At admission cholesterol and low-density lipoprotein (LDL) cholesterol levels in non-diabetic patients were significantly higher than diabetics. High-density lipoprotein (HDL) cholesterol levels were lower in patients with diabetes. At admission amongst patients with ischemic stroke and diabetes the mean serum creatinine was significantly higher compared to non-diabetic patients (1.35 ± 1.28 mg/dl vs. 1.07 ± 0.60 mg/dl, $p < 0.000$). Fibrinogen levels at admission were higher in diabetic patients.

32.2% of patients with ischemic and 15.5% of patients with hemorrhagic stroke had a history of previous stroke. A history of concomitant coronary heart disease/myocardial infarction occurred more frequently in patients with diabetes (Table II).

Mean admission glucose was 123.80 ± 58.10 mg/dl (124.31 ± 60.71 mg/dl in ischemic and 121.36 ± 43.56 mg/dl (NS) in hemorrhagic stroke patients). Mean admission glucose in all patients who died was significantly higher than in patients who survived. Amongst diabetic patients

Table II. Clinical characteristics of the population studied at admission to hospital

| Parameter | Non-diabetic | | Diabetic | | Total | | P-value | |
|--|--------------|---------------------|--------------------|---------------------|--------------------|---------------------|--------------------|----|
| | N | Mean \pm SD/% | N | Mean \pm SD/% | N | Mean \pm SD/% | | |
| Hypertension: | | | | | | | | |
| Ischemic stroke | 429 | 86.1 | 127 | 92.7 | 556 | 87.6 | 0.041 | |
| Hemorrhagic stroke | 99 | 84.6 | 12 | 100.0 | 111 | 86.0 | 0.215 | |
| Blood pressure at admission [mm Hg]: | | | | | | | | |
| Ischemic stroke | Systolic | 499 | 152.67 \pm 25.10 | 137 | 156.99 \pm 23.53 | 636 | 153.60 \pm 24.82 | NS |
| | Diastolic | 499 | 88.20 \pm 12.49 | 137 | 88.90 \pm 12.59 | 636 | 88.35 \pm 12.50 | NS |
| Hemorrhagic stroke | Systolic | 117 | 164.53 \pm 36.14 | 12 | 164.17 \pm 33.43 | 129 | 164.50 \pm 35.77 | NS |
| | Diastolic | 117 | 93.50 \pm 16.23 | 12 | 94.17 \pm 16.21 | 129 | 93.57 \pm 16.17 | NS |
| Cholesterol [mg/dl]: | | | | | | | | |
| Ischemic stroke | 406 | 184.36 \pm 40.97 | 107 | 168.83 \pm 42.30 | 513 | 181.12 \pm 41.69 | < 0.001 | |
| Hemorrhagic stroke | 48 | 183.42 \pm 50.83 | 9 | 194.00 \pm 50.18 | 57 | 185.09 \pm 50.43 | 0.555 | |
| HDL [mg/dl]: | | | | | | | | |
| Ischemic stroke | 398 | 50.50 \pm 56.80 | 106 | 36.61 \pm 13.89 | 504 | 47.58 \pm 51.17 | < 0.001 | |
| Hemorrhagic stroke | 46 | 45.23 \pm 17.43 | 9 | 43.84 \pm 14.71 | 55 | 45.01 \pm 16.89 | 1.000 | |
| LDL [mg/dl]: | | | | | | | | |
| Ischemic stroke | 398 | 118.37 \pm 35.93 | 106 | 109.30 \pm 32.35 | 505 | 116.50 \pm 35.38 | 0.025 | |
| Hemorrhagic stroke | 46 | 116.09 \pm 42.94 | 9 | 131.33 \pm 42.95 | 55 | 118.58 \pm 42.92 | 0.290 | |
| Creatinine at admission [mg/dl]: | | | | | | | | |
| Ischemic stroke | 451 | 1.08 \pm 0.51 | 118 | 1.38 \pm 1.33 | 569 | 1.14 \pm 0.77 | < 0.001 | |
| Hemorrhagic stroke | 95 | 1.04 \pm 0.92 | 11 | 1.02 \pm 0.27 | 106 | 1.04 \pm 0.87 | 0.171 | |
| Fibrinogen at admission [mg/dl]: | | | | | | | | |
| Ischemic stroke | 419 | 403.48 \pm 113.62 | 109 | 440.09 \pm 145.33 | 528 | 411.04 \pm 121.60 | 0.004 | |
| Hemorrhagic stroke | 98 | 413.55 \pm 147.00 | 11 | 517.12 \pm 144.80 | 109 | 424.00 \pm 149.44 | 0.009 | |
| Prior stroke: | | | | | | | | |
| Ischemic stroke | 157 | 31.8 | 47 | 34.3 | 204 | 32.3 | 0.606 | |
| Hemorrhagic stroke | 16 | 13.7 | 4 | 33.3 | 20 | 15.5 | 0.091 | |
| Coronary artery disease/myocardial infarction: | | | | | | | | |
| Ischemic stroke | 208 | 41.8 | 71 | 51.8 | 279 | 43.9 | 0.041 | |
| Hemorrhagic stroke | 21 | 17.9 | 5 | 41.7 | 26 | 20.2 | 0.065 | |

glucose levels were significantly higher than in non-diabetic patients (Table III). At admission blood samples for glycosylated hemoglobin (HbA_{1c}) were drawn for 122 (15.94%) patients. The mean HbA_{1c} in patients with ischemic stroke and without diabetes was 5.70 ±0.45% and in those with diabetes was 7.25 ±1.44%, and amongst patients with hemorrhagic stroke it was 5.78 ±0.40 vs. 5.90 ±0.00%, respectively. Insulin has been used in the treatment of patients with ischemic stroke and diabetes in 30.7% (*p* < 0.01), and hemorrhagic stroke patients in 66.7% (*p* < 0.01). In-hospital mortality in patients with ischemic stroke was 13.1% (non-diabetic 13.6%. and diabetic 10.9%, NS) and with hemorrhagic stroke was 24.0% (non-diabetic 21.4%, diabetic 50.0%, *p* = 0.038) (Table IV). The mean length of hospitalization in patients who survived was significantly longer than in those who died (ischemic 15.8 ±14.1; 9.6 ±9.8 days; *p* < 0.0001; hemorrhagic 25.3 ±19.0 vs. 14.3 ±15.1 days; *p* = 0.011). In patients with ischemic stroke in-hospital death occurred on the 10th day of treatment and in hemorrhagic stroke patients on the 14th. 60.7% of ischemic stroke patients were discharged to home. Every fourth patient with ischemic stroke was transferred to another health care facility. The duration of hospitalization was

similar among patients with ischemic stroke and with/without diabetes. Only one third of the patients with hemorrhagic stroke were discharged to home; the rest of patients were transferred to other health care facilities (Table V).

Mean serum glucose levels at admission are given in Table VI. The mean duration of hospitalization of patients with hemorrhagic stroke was significantly longer than that of patients with ischemic stroke (22.65 ±18.70 vs. 15.03 ±13.73; respectively *p* = 0.002). The duration of hospitalization was significantly longer in patients with hemorrhagic stroke and diabetes (Table VII). The only correlation was observed between admission glucose and the length of hospitalization of patients with hemorrhagic stroke and diabetes (*r* = -0.74, *p* = 0.006) (Table VIII). In multivariate analysis (Table IX), the risk factors for outcome in patients with ischemic stroke and without diabetes were age (*p* < 0.04; OR = 1.040), admission glucose level (*p* < 0.001; OR = 1.021) and eGFR using the Modification of Diet in Renal Disease (MDRD) equation (*p* = 0.007; OR = 0.979), and in diabetics they were female gender (*p* = 0.022; OR = 6.610), admission glucose level (*p* = 0.010; OR = 1.007), and eGFR using the MDRD equation (*p* < 0.001; OR = 0.937). In patients with hemorrhagic stroke and without

Table III. Serum glucose at admission in regard to the presence of diabetes

| Parameter | Non-diabetic | | Diabetic | | Total | | P-value | |
|-------------------------------------|--------------|---------------|----------|----------------|-------|---------------|---------|---------|
| | N | Mean ± SD/% | N | Mean ± SD/% | N | Mean ± SD/% | | |
| Serum glucose at admission [mg/dl]: | | | | | | | | |
| Ischemic stroke | 462 | 110.13 ±29.09 | 132 | 173.95 ±102.53 | 594 | 124.31 ±60.71 | < 0.001 | |
| Hemorrhagic stroke | 112 | 117.43 ±10.34 | 12 | 158.08 ±56.30 | 124 | 121.36 ±43.56 | 0.001 | |
| Serum glucose [mg/dl]: | | | | | | | | |
| Ischemic stroke | < 140 | 410 | 88.7 | 68 | 51.5 | 478 | 80.5 | < 0.001 |
| | 140–200 | 43 | 9.3 | 26 | 19.7 | 69 | 11.6 | |
| | ≥ 200 | 9 | 1.9 | 38 | 28.8 | 47 | 7.9 | |
| Hemorrhagic stroke | < 140 | 94 | 83.9 | 6 | 50.0 | 100 | 80.6 | 0.014 |
| | 140–200 | 12 | 10.7 | 4 | 33.3 | 16 | 12.9 | |
| | ≥ 200 | 6 | 5.4 | 2 | 16.7 | 8 | 6.5 | |

Table IV. Survival and mortality of the studied group

| Parameter | Non-diabetic | | Diabetic | | Total | | P-value | | |
|------------------|--------------------|-----------|----------|------|-------|------|---------|------|-------|
| | N | % | N | % | N | % | | | |
| End of treatment | Ischemic stroke | Discharge | 431 | 86.4 | 122 | 89.1 | 553 | 86.9 | 0.475 |
| | | Death | 68 | 13.6 | 15 | 10.9 | 83 | 13.1 | |
| | Hemorrhagic stroke | Discharge | 92 | 78.6 | 6 | 50.0 | 98 | 76.0 | 0.038 |
| | | Death | 25 | 21.4 | 6 | 50.0 | 31 | 24.0 | |

Table V. Outcome of the studied groups

| Parameter | Type of stroke | Total | | Survived | | Death | | P-value |
|-----------------------|--------------------|-------|------------|-----------------|------------|--------------------|------------|---------|
| | | N | Mean ± SD | N | Mean ± SD | N | Mean ± SD | |
| Length of stay [days] | Ischemic stroke | 637 | 15.0 ±13.8 | 553 | 15.8 ±14.1 | 84 | 9.6 ±9.8 | < 0.001 |
| | Hemorrhagic stroke | 129 | 22.7 ±18.7 | 98 | 25.3 ±19.0 | 31 | 14.3 ±15.1 | 0.011 |
| Parameter | Type of stroke | Total | | Ischemic stroke | | Hemorrhagic stroke | | P-value |
| | | N | % | N | % | N | % | |
| End of treatment | Discharge | 432 | 56.5 | 387 | 60.7 | 45 | 35.2 | < 0.001 |
| | Transfer | 218 | 28.5 | 166 | 26.1 | 52 | 40.6 | |
| | Death | 115 | 15.0 | 84 | 13.2 | 31 | 24.2 | |

Table VI. Mean serum glucose at admission in relation to presence of diabetes and type of stroke

| Type of stroke | | Diabetes | | | |
|--------------------|-----------------------------|---------------|----------------|--------------|-----------------|
| | | No | | Yes | |
| | | N | Mean ± SD | N | Mean ± SD |
| Ischemic stroke | Survived | 406 | 107.58 ±24.955 | 117 | 165.6 ±97.384 |
| | Death | 56 | 128.55 ±45.991 | 15 | 239.13 ±121.063 |
| | Whole group | 462 | 110.13 ±29.093 | 132 | 173.95 ±102.533 |
| | P-value (Mann-Whitney test) | 0.0005 | | 0.002 | |
| Hemorrhagic stroke | Survived | 87 | 109.55 ±34.369 | 6 | 119.67 ±14.123 |
| | Death | 25 | 144.84 ±47.793 | 6 | 196.5 ±56.843 |
| | Whole group | 112 | 117.43 ±40.335 | 12 | 158.08 ±56.297 |
| | P-value (Mann-Whitney test) | 0.0001 | | 0.004 | |

Table VII. Length of stay in relation to presence of diabetes

| Parameter | Outcome | Length of stay [days] | | P-value |
|-------------------------------------|-------------|-----------------------|--------------|---------|
| | | N | Mean ± SD | |
| Ischemic stroke without diabetes | Survived | 431 | 16.01 ±15.10 | < 0.001 |
| | Death | 68 | 10.41 ±10.57 | |
| | Whole group | 499 | 15.25 ±14.68 | |
| Ischemic stroke with diabetes | Survived | 122 | 15.27 ±9.74 | < 0.001 |
| | Death | 15 | 6.33 ±4.32 | |
| | Whole group | 137 | 14.29 ±9.70 | |
| Hemorrhagic stroke without diabetes | Survived | 92 | 24.60 ±19.37 | 0.077 |
| | Death | 25 | 15.60 ±16.15 | |
| | Whole group | 117 | 22.68 ±19.03 | |
| Hemorrhagic stroke with diabetes | Survived | 6 | 36.00 ±6.72 | < 0.001 |
| | Death | 6 | 8.83 ±8.16 | |
| | Whole group | 12 | 22.42 ±15.88 | |

diabetes the risk factors for outcome were age ($p = 0.013$; OR = 1.058) and admission glucose levels ($p = 0.003$; OR = 1.024). The study attempted to determine the admission glucose cut-off value for increased mortality. The predictive value of blood glucose level for mortality of ischemic stroke patients was estimated by receiver operating curve (ROC) analysis. The analysis was performed for diabetic and non-diabetic patients separately. In both cases, the area under the ROC curve (area under curve – AUC) was significantly higher than 0.5, which indicated the predictive value of blood glucose level. The optimal cut-off value was determined as the point of the ROC curve less distant from the ideal point (100% sensitivity and 100% specificity). The admission glucose cut-off value in predicting death in patients with ischemic stroke and without diabetes was above 113.5 mg/dl (52.63% sensitivity and 70.69% specificity). However, for patients with diabetes the admission glucose cut-off value for increased mortality was much higher: 210.5 mg/dl (60% sensitivity, 76.92% specificity). Due to the low number of events the admission glucose cut-off value in predicting death in patients with hemorrhagic stroke was not determined.

Discussion

Our study demonstrated that hyperglycemia on admission is associated with worsened clinical outcome and increased risk of in-hospital

Table VIII. Non-parametric correlations between presence of diabetes and length of stay

| Type of stroke | Parameter | Diabetes | |
|--------------------|-----------------|----------|--------------|
| | | No | Yes |
| Ischemic stroke | <i>r</i> | 0.02 | 0.09 |
| | <i>P</i> -value | 0.717 | 0.289 |
| Hemorrhagic stroke | <i>r</i> | -0.15 | -0.77 |
| | <i>P</i> -value | 0.122 | 0.006 |

death in ischemic and hemorrhagic stroke patients. Diabetes increased the risk of in-hospital death in hemorrhagic stroke patients, but not in ischemic stroke. Farrokhnia *et al.* [15] reported that the mean blood glucose concentration above 113 mg/dl predicted 30-day mortality in non-diabetic patients with stroke. However, for patients with diabetes, the value for such increased mortality was much higher at 185 mg/dl. In our work we also evaluated the admission glucose cut-off value for increased mortality. In patients with ischemic stroke and diabetes the cut-off value was 210.5 mg/dl, and in patients with ischemic stroke and without diabetes it was 113.5 mg/dl. This observation confirmed that a differential response to hyperglycemia existed between patients with and without diabetes. Several mechanisms may play a role in this finding. Patients with diabetes are more likely to receive insulin and oral

Table IX. Predictors of death in relation to presence of diabetes in stepwise logistic regression analysis (full model and elimination model)

| Type of stroke | Parameter | Full model | | Elimination model | |
|-------------------------------------|--------------------------|-------------------|-------|-------------------|-------|
| | | <i>P</i> -value | OR | <i>P</i> -value | OR |
| Ischemic stroke without diabetes | Age | 0.096 | 1.033 | 0.040 | 1.040 |
| | Gender (female vs. male) | 0.201 | 0.628 | | |
| | Glucose at admission | < 0.001 | 1.021 | < 0.001 | 1.021 |
| | eGFR by MDRD | 0.010 | 0.980 | 0.007 | 0.979 |
| | Systolic blood pressure | 0.077 | 0.987 | 0.081 | 0.987 |
| Ischemic stroke with diabetes | Age | 0.241 | 1.068 | | |
| | Gender (female vs. male) | 0.012 | 9.485 | 0.022 | 6.610 |
| | Glucose at admission | 0.011 | 1.007 | 0.010 | 1.007 |
| | eGFR by MDRD | 0.001 | 0.942 | < 0.001 | 0.937 |
| | Systolic blood pressure | 0.155 | 0.970 | 0.095 | 0.966 |
| Hemorrhagic stroke without diabetes | Age | 0.023 | 1.057 | 0.013 | 1.058 |
| | Gender (female vs. male) | 0.451 | 1.602 | | |
| | Glucose at admission | 0.008 | 1.024 | 0.003 | 1.024 |
| | eGFR by MDRD | 0.530 | 0.993 | | |

hypoglycemic treatment; however, all hypoglycemic drugs may influence glucometabolic health and endovascular inflammation [16]. In our study, patients with diabetes (30.7% with ischemic and 66.7% with hemorrhagic stroke) received insulin treatment. Furthermore, patients with diabetes may have reduced metabolic effects of hyperglycemia through chronic exposure to the evaluated glucose level. Then again, patients with diabetes have a higher glucose level that increased in-hospital mortality [3, 15]. Many factors have been identified through which hyperglycemia could increase cerebral damage in ischemic stroke [13]. Magnetic resonance imaging (MRI) has demonstrated that in patients with acute perfusion diffusion mismatch within 24 h of stroke onset, hyperglycemia correlated with reduced salvage of mismatch tissue from infarction, greater final size and worse outcome [13, 17–19]. Moreover, admission hyperglycemia impaired recanalization in patients with acute ischemic stroke, which may cause a worse clinical outcome after thrombolytic therapy [17, 20]. Decrease in perfusion in ischemic stroke has been associated with disturbances in coagulation and fibrinolysis and changes in blood rheology (increased blood viscosity, erythrocyte reduced susceptibility to deformation, increased tendency of red blood cells to form microaggregates) [13, 21–23]. Exposure of brain tissue to excessive levels of glucose resulted in disruption of the blood-brain barrier, anaerobic glycolysis, lactate accumulation, tissue acidosis, the formation of free radicals, release of excitatory neurotransmitters and calcium influx into the cell [5, 22–24]. Poorly controlled hyperglycemia reduces cerebral blood flow and oxygenation of tissues, and increases intracranial pressure, cerebral edema and neuronal death [14, 24–26]. These mechanisms, which are more severe in patients with diabetes and hemorrhagic stroke, perhaps increase mortality in hemorrhagic stroke, as in our work. Most of the studies have focused on the evaluation of hyperglycemia on admission and its impact on outcome and mortality in ischemic or hemorrhagic stroke [3, 8–10, 14]. In our work, we analyzed patients with ischemic and hemorrhagic stroke and with and without diabetes. Many studies have shown that hyperglycemia worsens the prognosis of ischemic stroke [3, 8–10]. Analysis of the GLIAS (GLyceria In Acute Stroke) study showed that persistent hyperglycemia above 155 mg/dl is commonly observed in patients with ischemic stroke and is associated with poorer outcome [27]. Hu *et al.* [3] found a significant association between initial glucose level and mortality in patients with ischemic stroke and without diabetes. In our study diabetes did not increase the risk of mortality in ischemic stroke. These differences between groups of patients

with and without diabetes and ischemic stroke is likely to result in different glucose cut-off values for increased mortality. Appelboom *et al.* [14] confirmed the relationship between admission glucose and mortality in patients with spontaneous intracerebral hemorrhage and severity of intraventricular extension. Other studies have also observed that hyperglycemia in patients with hemorrhagic stroke is an independent risk factor for mortality and poor clinical outcome and may affect the increase in the size of hematoma [28–31]. In addition, altered glucose metabolism may be due to inflammatory cell activation, as suggested by Tapia-Pérez *et al.* [32] on the basis of a relatively small retrospective study. Also serum lipids and kidney function may play a role in complications of diabetes [33]. In addition, increased serum level of soluble CXCL16 was independently associated with atherosclerotic ischemic stroke, as reported recently [34].

In our study diabetes was a risk factor for death in hemorrhagic stroke, in contrast to the study of Wang *et al.* [35]. They suggested that diabetes in Han Chinese patients with hemorrhagic stroke was not associated with increased mortality or functional outcome. It may be due to the genetic predisposition. Unlike in Caucasians, the minor allele C of rs11206510 was associated with increased LDL cholesterol levels in the Chinese Han population and conferred a risk of early-onset coronary artery disease and a significant risk of ischemic stroke [36]. Similarly, allele 936C of VEGF may serve as a genetic marker susceptible to diabetic neuropathy in Han Chinese, while allele 936T may be a protective genetic marker of it [37]. However, in the population of Southern China diabetes together with hypertension and hyperlipidemia was more prevalent in patients with lacunar infarction [38]. On the other hand, as decreased exercise capacity is an independent risk factor for major adverse cardiovascular events (MACE) in diabetes [39] as well as lower limb ischemia [40], it is also relevant for stroke. In recent studies, mainly registry or cohort studies, underlying the role of diabetes as a risk factor for death in stroke, the type of stroke is not elucidated [41–43], while in our relatively large sample we defined the type of stroke as Bhalla *et al.* [44] did in the South London Stroke Register. However, the Londoners with diabetes had poorer survival in ischemic stroke, while in general hemorrhagic stroke was associated with worse outcome up to 5 years after the event. In our study we focused on the in-hospital mortality and length of stay as well as the end of treatment (discharge or transfer to other health care facility). The duration of hospitalization was similar among patients with ischemic stroke and with/without diabetes. The length of hospital stay was significantly longer in patients with hemor-

hemorrhagic stroke and diabetes. About 30% of patients with hemorrhagic stroke were discharged to home; the rest of the patients were transferred to other health care facilities. Extending the duration of hospitalization of patients with hemorrhagic stroke up to 10 days is associated with increased costs of treatment. Treatment of hyperglycemia during hospitalization improves outcomes, reduces long-term disability and shortens duration of hospitalization. Then, hospitals have greater chances of achieving significant cost savings. Lower admission glucose level impacts the mortality in non-diabetic patients compared to patients with diabetes. We would like to stress that it is very important to control the level of glucose during hospitalization in all patients with stroke (with and without diabetes). In addition, not only the presence of diabetes but also, or even more importantly, hyperglycemia is a poor predictor of outcomes in both types of stroke. Kidney function, in particular in ischemic stroke, also has a great impact on the outcome.

In conclusion, hyperglycemia on admission is associated with worsened clinical outcome and increased risk of in-hospital death in ischemic and hemorrhagic stroke patients. Diabetes increased the risk of in-hospital death in hemorrhagic stroke patients, but not in ischemic stroke. The admission glucose cut-off value in predicting death in patients with ischemic stroke and diabetes was much higher than in non-diabetic patients. The duration of hospitalization of patients with hemorrhagic stroke and diabetes who died was longer compared to non-diabetic patients. Approximately 26.1% of patients with ischemic stroke were transferred to another health care facility to continue treatment or rehabilitation, compared to 40.6% of patients with hemorrhagic stroke.

Conflict of interest

The authors declare no conflict of interest.

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