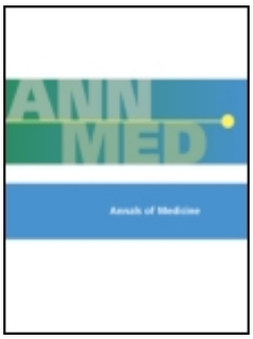

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ORIGINAL ARTICLE

Stroke in diabetic and non-diabetic patients: Course and prognostic value of admission serum glucose

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Abstract

Background, Aims. Whether diabetes mellitus affects the prognosis of stroke patients, and whether admission hyperglycemia influences prognosis similarly in diabetic as in non-diabetic patients is assessed controversially. The aims of the study were: 1) to compare the course of diabetic and non-diabetic acute stroke patients, and 2) to assess the influence of admission serum glucose levels on case fatality.

Methods. In 57 Austrian medical departments the hospital course of consecutive stroke patients was documented prospectively between June 1999 and October 2000.

Results. Two hundred and ninety-six (30%) of 992 patients had a history of diabetes mellitus. Intracerebral hemorrhage was more frequent in non-diabetic patients than diabetic (13% *versus* 5%, $P=0.0001$). Coronary heart disease was more frequent in diabetic than in non-diabetic patients (35% *versus* 24%, $P=0.0003$). The case fatality was 18% among non-diabetic and 16% among diabetic patients ($P=0.3559$). Among patients who were discharged alive, the Barthel Index increased from 50 to 90 in non-diabetic and from 45 to 75 in diabetic patients ($P=0.0403$). In non-diabetic patients, admission serum glucose >9.2 mmol/L was associated with a more than 4-fold increase in case fatality, compared with patients with serum glucose <5.7 mmol/L ($P<0.0001$).

Conclusions. Diabetic stroke patients need special care since they tend to have a poorer recovery than non-diabetic patients. Admission hyperglycemia in non-diabetic acute stroke patients predicts a poor prognosis.

Key words: *Case fatality, hyperglycemia, neurological outcome*

Introduction

Diabetes mellitus is a well-established independent risk factor for stroke (1–4). Stroke in diabetic patients has been found to be associated with high case fatality in a long-term study (5).Whether diabetes mellitus affects the short-term prognosis of acute stroke patients is controversial (5–12). A poor outcome in acute stroke has been linked to admission hyperglycemia (13,14). Whether this effect is equally important in diabetic as in non-diabetic patients is controversial (6,13).Thus, the aims of the present study were 1) to compare the in-hospital course in acute stroke patients with and without diabetes mellitus, and 2) to assess the influence of admission serum glucose levels on case fatality depending on presence or absence of diabetes mellitus.

Patients and methods

The Austrian Stroke registry is a prospective multi-center study (15). Medical departments all over Austria participated in the trial documenting the in-hospital course of consecutive patients with acute stroke from June 1999 to October 2000. All consecutive patients with acute stroke were documented and evaluated. Excluded were patients with transient ischemic attacks, cerebral tumor, sub- or epidural hemorrhage or other conditions imitating ischemic stroke. Additionally, patients were excluded if they

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Abbreviations

AF	atrial fibrillation
BI	Barthel Index
CAD	coronary artery disease
Hyp	arterial hypertension
ICH	intracerebral hemorrhage
NIHSS	National Institute of Health Stroke Scale
RS	Rankin scale

Key messages

- Diabetic stroke patients need special care since they tend to have a poorer recovery than non-diabetic patients.
- Admission hyperglycemia in non-diabetic acute stroke patients predicts a poor prognosis.

were transferred to other departments within 3 days after admission or if the onset of stroke was >3 days before admission. There was not any common protocol on how to manage diabetic patients in the acute phase of stroke. Using specific forms the following data were recorded by the treating physicians:

1. *Baseline characteristics*: Age, sex, weight, height, blood-pressure, heart-rate, random serum glucose level at hospital admission, hematocrit, cholesterol, fibrinogen and electrocardiogram within 24 hours of admission. Glycated hemoglobin was not recorded.
2. *Vascular risk factors and co-morbid conditions*: Coronary heart disease, other heart disease (dilated or hypertrophic cardiomyopathy, valvular heart disease, congenital heart disease), previous stroke, hypertension, obstructive pulmonary disease, current smoking, malignancy and dementia. Diabetes was assessed as present in patients with a history of diabetes or treatment with antidiabetic drugs.
3. *Neurological findings*: Type and location of the stroke were assessed. On admission and at discharge the Barthel Index (BI) scoring from 0 to 100 points (16), the Rankin Scale (RS) (17) and the National Institute of Health Stroke Scale (NIHSS) (18) were applied.
4. *Stroke-related neurological complications*: Cerebral edema (as seen on cerebral computed tomography or magnetic resonance imaging), hydrocephalus, recurrent stroke, symptomatic intracerebral bleeding and seizures.
5. *Medical complications*: Pneumonia (fever, leukocytosis, infiltrate on chest X-ray), urinary tract infection (leukocytosis, positive findings on urine culture), sepsis (fever, leukocytosis, positive findings on blood culture, organ involvement), deep vein thrombosis (demonstrated by venography or ultrasound), pulmonary embolism (demonstrated by helical computed tomography), pulmonary edema (clinical signs, pulmonary congestion on chest X-ray) and extracerebral bleeding.
6. *Treatment during hospitalization and at discharge*: Parenteral fluid, parenteral nutrition, antibiotics, antipyretics, insulin, antihypertensives, heparin, acetylsalicylic acid or antiplatelet drugs, thrombolysis, neurosurgical therapy and transfer to an intensive care unit. The medical therapy at discharge was registered. Dietary treatment only for diabetic patients was not registered.

Statistical analyses were performed by using the statistical software package SYSTAT version 10 (SPSS Inc, Chicago Ill. USA). Continuous data were expressed as median values and quartiles. Non-continuous data were expressed as percent. In univariate descriptive analysis the Kruskal-Wallis-test and the Pearson chi-square test were used. During univariate testing a total of 125 tests have been calculated and so the level of significance was chosen to be $\alpha=0.0004$ according to the Bonferroni correction. All tests were two-sided.

Stepwise multivariable logistic regression modeling was used to assess the prognostic significance of predictor variables for case fatality. Continuous variables were plotted against the outcome. In order to satisfy the assumption of linearity they were transformed to binary variables. For virtually all variables a clear threshold could be identified which indicated an increased case fatality. For age, this was >75 years, for mean arterial blood pressure <80 mmHg, for heart rate >100 bpm, for blood glucose >7 mmol/L, for hemoglobin <7.1 mmol/L, for serum cholesterol <4 mmol/L, for serum creatinine >125 μmol/L and for fibrinogen >11 μmol/L. The BI showed an increased risk for the value zero at admission *versus* all higher values. For the RS a value of 5 at admission had a higher risk than all lower values. The distribution of the NIHSS suggested 3 categories: patients with values above 21 had a moderate risk while those who were comatose had the highest risk. The coding for binary variables followed the 'partial method' using

'0' for the absence and '1' for the presence of the condition in question. In analogy to that, the binary variables derived from the continuous data were coded with '0' for the absence and '1' for the presence of the criteria shown above. The NIHSS was coded with '0' for values up to 21, with '1' for values above 21 and with '2' for the comatose patients. Sex was coded with '1' for male and '2' for female gender. In order to check for 'influential observations' the variable centre was forced into the model and declared as a categorical variable with 'dummy' coding. The following independent variables were retained for the analysis: centre, sex, age groups, intracerebral bleeding, localization: brainstem, BI, RS, NIHSS, previous stroke, coronary artery disease, hypertension, diabetes, atrial fibrillation, obstructive pulmonary disease, malignancy, mean arterial pressure, heart rate, glucose, hemoglobin and creatinine. A forward stepwise selection of the variables was chosen for the multivariable logistic regression. The probability for entry of a variable was set at 0.05 and for the removal of a variable at 0.10.

Results

The Austrian Stroke Registry recruited 1100 patients with acute stroke in 57 hospital departments. Excluded were patients who were transferred to other departments within 3 days after admission ($n=55$) or in whom the onset of stroke was >3 days before admission ($n=39$), or whose data forms were incomplete ($n=14$). Therefore, 992 patients remained for evaluation. These 992 patients were hospitalized for a median of 14 days (range 1–92 days). Two hundred and ninety-six patients (30%) of the 992 patients had a history of diabetes mellitus. Cerebral computed tomography was carried out in 98% of diabetic and 95% of non-diabetic patients.

Baseline characteristics (Table I). Diabetic patients had more ischemic strokes and less intracerebral hemorrhages than non-diabetics. There were no differences between the groups with respect to the localization of stroke or to severity as estimated by neurological scores such as the BI, RS or NIHSS.

As expected, admission serum glucose levels were higher in patients with diabetes. All other laboratory parameters were similar in the two groups. The frequency of coronary heart disease was higher in diabetic than in non-diabetic patients; for hypertension the level of statistical significance was not quite reached. In the subgroup of patients with hypertension, stroke was due to intracerebral hemorrhage in 5% of the diabetics and in 14% of the non-diabetic patients ($P=0.0001$).

Stroke-related neurological and medical complications (Table II). No differences were found in the incidence of neurological complications between diabetic and non-diabetic patients. Among the medical complications, urinary tract infection occurred somewhat more frequently in diabetic than in non-diabetic patients.

Treatment during hospitalization and at discharge (Table III). As expected, diabetic patients received insulin more frequently than non-diabetics. The higher prescription rate of antibiotics – consistent with the slightly higher incidence of infections – and antihypertensive drugs did not quite reach the level of statistical significance. At discharge from hospital, patients with diabetes were prescribed more antidiabetics and antihypertensive drugs, in particular angiotensin-converting-enzyme (ACE) inhibitors and diuretics, reflecting the higher cardiovascular co-morbidity or the higher prescription rate of ACE-inhibitors in diabetic patients. In the 4 non-diabetic patients (1%) who were discharged with antidiabetic therapy, diabetes mellitus was diagnosed during hospitalization.

Outcome: The in-hospital case fatality did not differ between groups and was 18% among the non-diabetic and 16% among the diabetic patients ($P=0.3559$). For multivariable analysis a total of 88 patients with missing values of any of the variables chosen had to be excluded, leaving 904 patients. Case fatality was 17% in this population, showing no change from the original group of 992 patients. Multivariable logistic regression analysis identified the following characteristics as significant predictors of case fatality: BI of zero on admission (odds ratio 5.30, 95% CI 3.10–9.08, $P<0.0001$), NIHSS >21 or comatose on admission (odds ratio 3.13, 95% CI 2.26–4.32, $P<0.0001$), age >75 years (odds ratio 3.15, 95% CI 1.85–5.37, $P<0.0001$), heart rate >100/min (odds ratio 2.15, 95% CI 1.26–3.66, $P=0.0049$), obstructive pulmonary disease (odds ratio 2.58, 95% CI 1.03–6.48, $P=0.0442$) and creatinine >125 μmol/L (odds ratio 1.84, 95% CI 1.00–3.37, $P=0.0479$).

Among patients who were discharged alive, the median of the BI increased from 50 to 90 in non-diabetic and from 45 to 75 in diabetic patients ($P=0.0403$). The median of the RS score decreased from 4 to 3 in diabetic as well as non-diabetic patients. The proportion of patients in RS score 0–1, however, was higher in non-diabetic patients than

Table I. Baseline characteristics of 992 diabetic and non-diabetic patients with acute stroke

	Non-diabetic patients, n=696	Diabetic patients, n=296	P value
Demography			
Age years[a]	77 (69–83)	76 (68–82)	0.3539
Female *n* (%)	392 (56)	175 (59)	0.4148
Current smoking *n* (%)	64 (9)	25 (8)	0.7054
Duration of hospitalization days[a]	13 (9–20)	14 (9–22)	0.0459
Body Mass Index[a]	25.7 (23–28)	26.4 (24–29)	0.0105
Type and location of stroke			
Ischemic stroke *n* (%)	546 (78)	259 (88)	0.0009
Intracerebral hemorrhage *n* (%)	89 (13)	14 (5)	0.0001
Lacunar stroke *n* (%)	55 (8)	20 (7)	0.5323
Hemispheric stroke *n* (%)	304 (44)	136 (46)	0.5106
Cerebellar stroke *n* (%)	28 (4)	20 (7)	0.0663
Brainstem stroke *n* (%)	67 (10)	28 (10)	0.9348
Neurological scores			
Barthel Index[a]	35 (5–75)	25 (5–65)	0.1300
Rankin scale[a]	4 (2–5)	4 (3–5)	0.0065
Comatose patients *n* (%)	84 (12)	28 (10)	0.2959
NIHSS (non-comatose patients) [a]	6 (3–13)	7 (4–14)	0.2024
Findings on admission			
Systolic blood pressure mmHg[a]	160 (140–180)	162 (140–190)	0.1131
Diastolic blood pressure mmHg[a]	90 (80–100)	85 (80–100)	0.3821
Heart rate beats/min[a]	80 (70–94)	82 (72–97)	0.0377
Serum glucose mmol/L[a]	6.3 (5.4–7.8)	10.0 (7.5–13.8)	$<$0.0001
Hemoglobin g/L[a]	140 (130–150)	138 (130–150)	0.2111
Cholesterol mmol/L[a]	5.5 (4.7–6.4)	5.6 (4.6–6.5)	0.8249
Creatinine micromol/L[a]	88.4 (75.1–106.1)	88.4 (79.6–127.3)	0.3673
Fibrinogen g/L[a]	3.71 (3.20–4.50)	3.89 (3.20–4.64)	0.2599
Co-morbidities			
Atrial fibrillation/flutter *n* (%)	210 (30)	94 (32)	0.6204
Coronary heart disease *n* (%)	168 (24)	105 (35)	0.0003
Hypertension *n* (%)	458 (66)	221 (75)	0.0060
Previous stroke *n* (%)	183 (26)	98 (33)	0.0292
Other heart disease *n* (%)	121 (17)	52 (18)	0.9447
Obstructive pulmonary disease *n* (%)	40 (6)	14 (5)	0.5181
Dementia *n* (%)	57 (8)	32 (11)	0.1862
Malignancy *n* (%)	32 (5)	14 (5)	0.9279

[a] median (inter-quartile range)

Table II. Complications in diabetic and non-diabetic patients with acute stroke

	Non-diabetic patients, n=696	Diabetic patients, n=296	P value
Stroke-related neurological complications			
Cerebral edema *n* (%)	83 (12)	30 (10)	0.4167
Hydrocephalus *n* (%)	3 (0.4)	0	0.2579
Recurrent stroke *n* (%)	19 (3)	15 (5)	0.0640
Epileptic seizure *n* (%)	19 (3)	6 (2)	0.5181
Symptomatic intracerebral bleeding *n* (%)	26 (4)	10 (3)	0.7830
Any neurological complication *n* (%)	125 (18)	55 (19)	0.8162
Medical complications			
Pneumonia *n* (%)	96 (14)	39 (13)	0.7952
Urinary tract infection *n* (%)	85 (12)	57 (19)	0.0037
Sepsis *n* (%)	9 (1)	3 (1)	0.7124
Deep venous thrombosis *n* (%)	6 (1)	1 (0.3)	0.3667
Pulmonary embolism *n* (%)	5 (1)	4 (1)	0.3360
Pulmonary edema *n* (%)	49 (7)	26 (9)	0.3418
Extracerebral bleeding *n* (%)	2 (0.3)	4 (1)	0.0479
Any medical complication *n* (%)	200 (29)	108 (36)	0.0157

Table III. Treatment in diabetic and non-diabetic patients with acute stroke

Treatment during hospitalization	Non-diabetic patients, n=696	Diabetic patients, n=296	P value
Parenteral fluid *n* (%)	554 (80)	227 (77)	0.3057
Antibiotics *n* (%)	158 (23)	91 (31)	0.0075
Antipyretics *n* (%)	34 (5)	22 (7)	0.1116
Insulin *n* (%)	17 (2)	82 (28)	<0.0001
Antihypertensive therapy *n* (%)	285 (41)	148 (50)	0.0085
Heparin *n* (%)	446 (64)	200 (68)	0.2916
Parenteral nutrition *n* (%)	80 (11)	35 (12)	0.8818
Intensive care *n* (%)	76 (11)	22 (7)	0.0921
Thrombolysis *n* (%)	4 (1)	2 (1)	0.8511
Acetylsalicylic acid/antiplatelets *n* (%)	444 (64)	188 (64)	0.9332
Neurosurgery	3 (1)	0	0.2579
Treatment at discharge[a]	n=515	n=227	
Acetylsalicylic acid/antiplatelets *n* (%)	324 (63)	146 (64)	0.7144
Insulin/antidiabetics *n* (%)	4 (1)	127 (56)	<0.0001
Beta-blockers *n* (%)	83 (16)	46 (20)	0.1695
ACE-inhibitors *n* (%)	205 (40)	131 (58)	<0.0001
Diuretics *n* (%)	102 (20)	82 (36)	<0.0001
Ca-antagonists *n* (%)	102 (20)	59 (26)	0.0596
Oral anticoagulation *n* (%)	72 (14)	20 (9)	0.0489

[a] Only patients who were alive and not transferred to other departments were included.

diabetic (14% *versus* 7%, P=0.004). The median of the NIHSS decreased from 5 to 2 in diabetic as well as non-diabetic patients.

Hyperglycemia at admission: Median admission serum glucose level was 7.1 mmol/L (Q1: 5.7 mmol/L, Q3: 9.2 mmol/L). Patients with serum glucose levels above the median more often had diabetes mellitus (49% *versus* 12%, $P<0.0001$), and a lower BI (25 *versus* 45, $P<0.0001$) at admission. Admission serum glucose levels were lowest (6.7 mmol/L) in alert patients, 7.9 mmol/L in benumbed, 7.7mmol/L in obtunded and highest (8.6 mmol/L) in unresponsive patients ($P<0.0001$). Case fatality increased with increasing levels of serum glucose (Figure 1). This increase was more pronounced in non-diabetic than in diabetic patients. In non-diabetic patients, admission serum glucose >9.2 mmol/L was associated with a more than 4-fold crude increased case fatality, compared to patients with serum glucose <5.7 mmol/L ($P<0.0001$). When controlled for level of

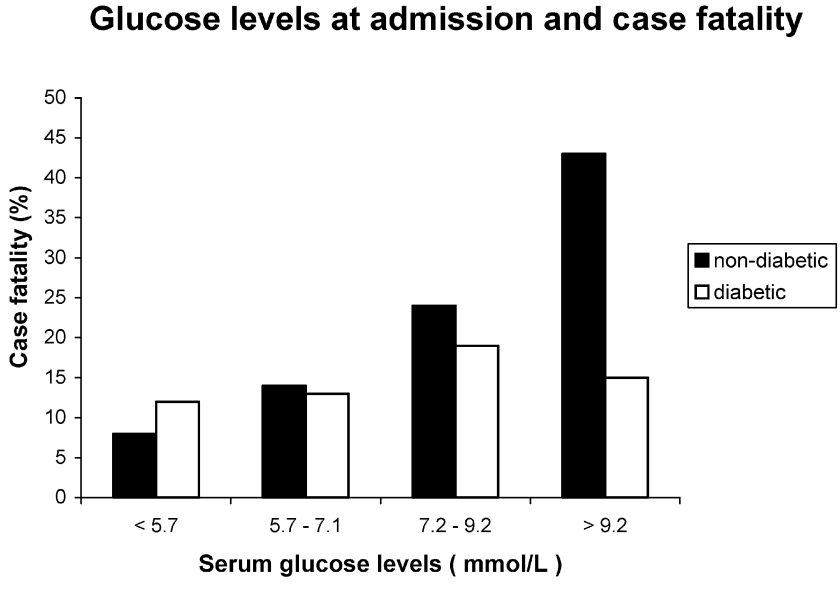

Figure 1. Association of admission serum glucose levels with case fatality in diabetic and non-diabetic patients.

consciousness, there was a trend of a higher case fatality in alert patients with increasing serum glucose levels ($P=0.0115$).

Discussion

This study shows that the in-hospital case fatality of stroke did not differ between diabetic and non-diabetic patients. There was a tendency, however, of a poorer recovery in diabetic than in non-diabetic patients as reflected by a higher disability (BI) at discharge. Admission serum glucose levels were higher in patients who died during hospitalization than in patients who were discharged alive. In non-diabetic patients admission serum glucose levels >9.2 mmol/L were associated with a more than 4-fold increased case fatality, compared with patients with serum glucose levels <5.7 mmol/L.

Diabetic patients, particularly women, have a high risk of stroke (1–4). Whether diabetes influences the prognosis after stroke is controversial (Table IV). Diabetes has been shown to increase the short-term (6,8–11) and long-term (5) case fatality after stroke. In two further studies (7,12) however, the 3-month case fatality did not differ between diabetic and non-diabetic patients. These findings are similar to the results of the present study, which found no differences in the case fatality between diabetic and non-diabetic patients. The controversy about diabetes and stroke case fatality may be due to differences in the age of the studied patients, in the prevalence of diabetes and co-morbid conditions, in the duration of follow-up and whether only patients with ischemic strokes or also patients with intracerebral hemorrhage were included (Table IV). The prevalence of 30% diabetes in the present study is much higher than the 15%–22% reported previously (5,6,8–10,12,19) and may reflect that the study included patients admitted only to medical and not to neurological departments. During the same period, the prevalence of diabetes in acute stroke patients admitted to neurologic stroke units was 24% (20).

Differences in the recovery of stroke between diabetic and non-diabetic patients were detected in the present study and in previous studies. Neurological outcome was worse (11), speed of recovery was slower (7,10) and recovery of motor function was poorer (12) in diabetic compared to non-diabetic patients. This may be explained by the higher prevalence of coronary heart disease, peripheral arterial occlusive disease, neuropathy, retinopathy, nephropathy and pre-stroke disability in diabetic compared to non-diabetic patients.

Diabetic patients had less intracerebral hemorrhages than non-diabetic. Although diabetes has been identified as a risk factor for cerebral hemorrhages by epidemiologic studies (21), the relatively lower proportion of cerebral hemorrhages among diabetic compared to non-diabetic patients has been shown in previous reports (6,8,10,12,19). This phenomenon may due to vessel wall abnormalities such as thickened capillary basement membranes of small cerebral vessels or endothelial proliferation (22–24). These vascular changes might prevent hemorrhages.

Our findings confirm previously described associations between acute hyperglycemia in stroke patients and a high short-term case fatality and poor functional recovery (7,10,13,14,25–28). The reasons for the increased case fatality in patients with admission hyperglycemia are not completely understood, but there are strong indications that hyperglycemia may be directly toxic to the ischemic brain since it leads to intracellular acidosis (29). 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 (25). Furthermore, hyperglycemic patients are relatively deficient in insulin and not likely to receive insulin, especially when they are non-diabetic. Possibly, it is still assumed erroneously that glucose is 'good for the brain'. Insulin deficiency leads to both reduced peripheral uptake of glucose and increasing circulating free fatty acids. On the other hand, non-diabetic

Table IV. Prevalence of diabetes, co-morbid conditions and case fatality in studies of acute stroke patients

Author/year	Patients (*n*)	Mean age (years)	Diabetes (%)	CAD[a] (%)	AF[b] (%)	Hyp[c] (%)	ICH[d] (%)	Case fatality diabetic/ non-diabetic patients (%)
(5) 1990	705	72	17	29	18	51	9	40/20
(6) 1988	428	72	18	26	21	54	10	28/15
(8) 1992	176	69	17	nr[e]	nr[e]	57	16	25/11
(9) 1992	327	68	22	nr[e]	17	52	0	39/9
(10) 1994	1135	74	21	30	24	49	6	24/17
(12) 2003	4481	72	21	nr[e]	18	49	11	20/22
present study	992	75	30	28	31	68	10	16/18

[a]=Coronary artery disease, [b]=Atrial fibrillation, [c]=Arterial hypertension, [d]=Intracerebral hemorrhage, [e]=not reported

patients who develop hyperglycemia in acute stroke are likely to have undiagnosed diabetes mellitus. (8,10,11,14). In the present study at least 1% of the non-diabetic patients were diagnosed as having diabetes mellitus during hospitalization since they were discharged with antidiabetic therapy (Table III). Patients with hyperglycemia or undiagnosed diabetes mellitus have a higher risk of vascular disease than patients with normal glucose levels (30), which could contribute to the higher case fatality from cardiovascular diseases. Furthermore, hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke due to release of higher levels of stress hormones like cortisol or norepinephrine.

Whereas the association between hyperglycemia and poor outcome is a consistent finding in non-diabetic stroke patients, this association has not been found consistently in diabetic patients, as in the present study (6,10,13). Possible explanations for these discrepancies are the low number of diabetic patients and the fact that diabetic patients are more likely to receive therapy for hyperglycemia. Glucose-lowering therapy will reduce the amount of glucose available to enter into the brain and thereby might reduce cerebral acidosis. In animal studies it has been shown that administration of insulin reduces the size of the infarct and improves prognosis after stroke (29,31). Whether in humans glucose lowering at the time of stroke can improve outcome, remains to be elucidated (32).

Limitations of the study are the lack of long-term follow-up data, that serum glucose was only registered once at admission, that no data about the quality of serum glucose management during hospitalization were recorded and possibly selection bias of the reported patients.

We conclude that diabetic stroke patients need special care since they tend to have a poorer recovery than non-diabetic patients. Admission hyperglycemia, especially in non-diabetic stroke patients is an indicator of an increased case fatality.

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