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Hyperglycaemia in acute ischaemic stroke is associated with an increased 5-year mortality

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Abstract

Background: admission hyperglycaemia (HG) is associated with worse prognosis and higher mortality within 3 months after stroke. Reports on long-term mortality are inconsistent.
Objective: to evaluate the influence of admission HG [blood glucose (BG) levels >8 mmol/L] on long-term mortality after ischaemic stroke (IS) and transient ischaemic attack (TIA).
Methods: consecutive patients with IS or TIA, admitted from January 1997 until December 2002, were retrospectively screened. BG was measured within 3 days from onset of symptoms. Information on the date of death was obtained within 10 years after onset.
Results: a total of 509 patients (78% IS; 22% TIA) were included. Admission HG was present in 28% and 18% of the IS and TIA patients, respectively ($P = 0.05$). Mean admission BG was 7.6 ± 3.2 mmol/L in the IS and 6.7 ± 2.3 mmol/L in TIA ($P = 0.002$). During a mean observation of 66 ± 35 months, the overall 1- and 10-year mortality rate was 12% and 51% in IS compared to 4% and 38% in TIA patients ($P = 0.004$). Normoglycaemic IS patients had a longer median survival than those with HG (113 vs 84 months, $P = 0.04$). Admission HG did not affect the mortality rates in TIA patients.
Conclusion: admission HG is associated with greater mortality rates up to 5 years after stroke but does not influence the survival of TIA patients.

Keywords: *hyperglycemia, ischemic stroke, long-term mortality, elderly*

Background

Diabetes mellitus (DM) is a well-recognised, independent predictor of ischaemic stroke (IS) incidence [1]. Hyperglycaemia (HG) is present in up to 49% of IS patients without a pre-existing diagnosis of diabetes, and is associated with a higher mortality within 1 month post-stroke [2]. Reports on long-term mortality combine data for diabetic and non-diabetic patients and the follow-up period has been limited to the first year post-stroke [3]. It has previously been reported that more than half of patients with transient ischaemic attacks (TIAs) or minor IS without a previously established diagnosis of DM, have impaired glucose tolerance (IGT) or diabetic glucose tolerance [4]. IGT in TIA patients has further been associated with an increased risk for stroke compared to patients with normal baseline glucose values [5]. The Group of Pharmacoepidemiology in the Elderly (GIFA) study reported blood glucose (BG) level at admission to be directly associated with in-hospital mortality after TIA or minor stroke [6].

Here, we evaluated the influence of admission HG on long-term mortality after acute IS and TIA. Retrospective investigation of 509 IS and TIA patients, was performed during a period of 10 years. The presence of IS and TIA enables the study of the whole spectrum of acute ischaemic cerebrovascular diseases. The level of BG used to define admission HG was 8 mmol/L since it is a threshold over which poorer outcome has previously been described [7].

Methods

The local ethical committee approved this study. Consecutive IS and TIA patients ($n = 620$) admitted to the Department of Neurology of the Karolinska University Hospital, Huddinge, during the period January 1997 to December 2002 were retrospectively screened for inclusion. No pre-selection of the patients was performed, since all who had experienced a stroke in the area of responsibility of the hospital were admitted to our department regardless of age, stroke severity or co-morbid diseases. Patients with a final diagnosis of cerebral haemorrhage (I 61), vertigo (R 42) and cerebrovascular disease not specified as haemorrhage or infarction were excluded ($n = 39$). Patients with no measurement of BG

Table 1. Baseline characteristics of patients

	ICVD ($n = 509$)	Ischaemic stroke ($n = 395$)	TIA ($n = 114$)	P-value
Age (years) (mean ± SD)	69.7 ± 11.4	70.2 ± 11.5	68.1 ± 10.8	0.06
Male gender, *n* (%)	287 (56)	227 (57)	60 (53)	0.39
Current smoking	117 (23)	88 (22)	29 (25)	0.52
Atrial fibrillation	98 (19)	86 (22)	12 (11)	0.07
Hypertension	269 (53)	206 (52)	63 (55)	0.46
Known hyperlipidaemia	112 (22)	79 (20)	33 (29)	0.05
Diabetes mellitus	91 (18)	76 (19)	15 (13)	0.16
Admission hyperglycaemia	130 (26)	109 (28)	21 (18)	0.05

The numbers in the parentheses indicate the percentages.

value within 3 days from the initiation of symptoms were also excluded ($n = 72$). Finally, 509 consecutive patients who had a diagnosis of cerebral infarction (I 63) or TIA (G 45) using the WHO criteria were included in the study. All patients were seen by a neurologist and had clinically relevant investigations performed, including at least brain imaging with computed tomography (CT) as well as in many cases ancillary diagnostic investigations including duplex ultrasonography of the carotid and vertebral arteries, echocardiography and standardised blood tests.

Mortality within IS and TIA was studied in association with acute HG. The observational period extended from January 1997 to December 2007. Information on the date of death was obtained from electronic records, and no data are missing. Risk factors investigated as predictors of mortality were age ≥70 years, male gender, DM, atrial fibrillation (AF), smoking, hypertension (HT), hyperlipidaemia and admission HG. DM was considered present when a patient had known DM at admission. AF was considered as a risk factor when previously diagnosed or present on the admission ECG. Data on admission ECG were missing in few patients ($n = 18$). HT was present when a patient was on anti-hypertensive treatment at the time of admission or when HT was diagnosed during the hospital stay by repeated detection of blood pressure ≥140/90 mmHg. Hyperlipidaemia was considered present when a patient was on statin treatment or a fasting total cholesterol value >7 mmol/L was established at admission. All patients smoking any kind of tobacco on daily basis were coded as current smokers and former smokers were coded as non-smokers. Data on smoking habits were missing in IS ($n = 43$) and in TIA patients ($n = 12$), accounting for 11% of all subjects. All data including laboratory investigation and dates of symptom initiation and death were extracted from patients' medical records. In 88% of the cases (84% of IS and 95% of TIA), the plasma glucose concentration was measured within 24 h after admission.

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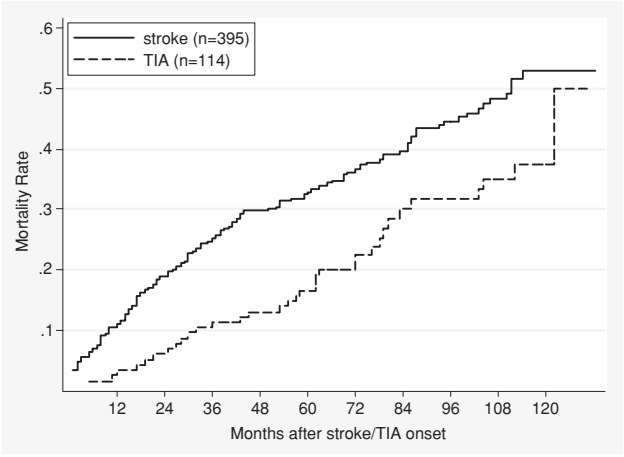
Statistical analysis

Stata statistical software was used for analysis. Demographic and baseline characteristics are presented as means ± SD and as percentages. Associations of acute HG, other risk factors and baseline characteristics in IS and TIA were assessed by the Mann–Whitney test for continuous variables and the chi-squared test for categorical variables. Time to death was examined with Kaplan–Meier analysis, and differences in survival between hyperglycaemic and normoglycaemic patients were assessed for statistical significance with the log-rank test. Cox proportional hazards regression analysis was performed to calculate the hazard ratios (HRs), with 95% confidence intervals (CIs), for the effect of age, gender, HT, DM, current smoking, hyperlipidaemia and AF on mortality. The assumption of proportional hazards was held for all variables in this model. The HR associated with admission HG was estimated in a separate model by entering age and gender as significant prognostic variables. In order to investigate possible interactions between gender and admission HG, the IS group was stratified for age and considered as a present risk factor in patients ≥70 years old at the onset of disease. The group of normoglycaemic men was the reference to each age group. Uncorrected probability values <0.05 were considered statistically significant.

Results

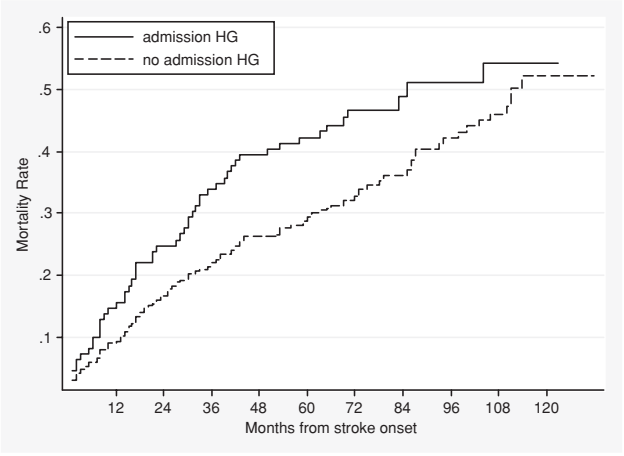
Baseline characteristics of the 509 patients included in the study are listed in Table 1. Age range was 23–94 years in IS ($n = 395$) and 44–86 years in TIA patients ($n = 114$), with a mean age of 70 and 68 years respectively. Slightly more than half were men in both groups. The mean admission glucose level in IS (7.6 ± 3.2 mmol/L) was higher than in TIA patients (6.7 ± 2.3 mmol/L, $P = 0.002$). Admission HG was present in 28% of IS and in 18% of TIA patients ($P = 0.05$). Hyperglycaemic IS patients were less often smokers (14% vs 26%, $P = 0.01$) and had more often hyperlipidaemia (27% vs 17%, $P = 0.05$) and DM (29% vs 15%, $P = 0.02$) than normoglycaemic subjects, while age, gender and other risk factors did not differ significantly between the groups (not shown).



Cumulative mortality rate (%)	1Y	2Y	5Y	10Y	P-value*
Stroke	12	20	33	51	0.004
TIA	4	7	17	38	

* P-value was calculated with the log-rank test

Figure 1. Kaplan–Meier mortality curves in stroke and TIA survivors.



Cumulative mortality rate (%)	1Y	2Y	5Y	10Y	P-value
IS with admission HG	16	25	42	54	0.04
IS without admission HG	9	18	29	50	

* P-value was calculated with the log-rank test

Figure 2. Kaplan–Meier mortality curves in hyperglycaemic versus normoglycaemic IS survivors. HG indicates hyperglycaemia.

Thus, more than two-thirds (71%) of the hyperglycaemic IS patients had no prior evidence of diabetes.

During the mean observation of 66 ± 35 months, 200 patients died. The overall mortality rate at 1 month after symptom onset was 4% in IS and 0% in TIA patients. The 1-, 5- and 10-year mortality rates were 12%, 33% and 51% in IS compared to 4%, 17% and 38% in TIA patients, respectively (Figure 1 , $P = 0.004$ with the log-rank test).

IS patients with and without admission HG had a median survival of 84 and 113 months, respectively. When patients who had been sampled within 24 h from symptom onset were analysed, the difference in median survival favouring normoglycaemic subjects was even greater (69 vs 109 months, respectively). Mortality rates at 1, 2 and 5 years from stroke onset were 9, 18 and 29% in normoglycaemic and 16, 25 and 42% in hyperglycaemic subjects, respectively (Figure 2, $P = 0.04$ with the log-rank test). The annual mortality rate in the hyperglycaemic group remained close to 2% after the fifth year, and reached an overall 10-year mortality rate of 54%. In normoglycaemic subjects, the overall mortality rate increased from 29 to 50% from the fifth year to the end of study (Figure 2). Admission HG did not influence the mortality rates in TIA. The assumption of proportional hazards held for all variables. Age was a significant predictor of mortality in both IS (HR 2.8; 95% CI 1.97–3.97; $P < 0.0001$) and TIA patients (HR 4.9; 95% CI 2.24–10.71; $P < 0.0001$) using univariate analysis. Tobacco use, AF, HT, DM and hyperlipidaemia did not predict mortality in any of the two groups. After adjusting for age and gender, the HR attributed to admission HG was 1.3 in IS, but the observation did not reach statistical significance (95% CI 0.96–1.84; $P = 0.08$) possibly on account of the insufficient sample size. Among the relatively younger subjects (age <70 years; $n = 159$, 39 died, mean observation period 74 ± 32 months), admission HG was associated with higher mortality in both women (HR 3.2; 95% CI 1.32–7.86; $P = 0.01$) and men (HR 2.2; 95% CI 1.04–4.65; $P = 0.04$). Admission HG in older patients had no significant effect on time to death in men or women.

Discussion

Here we demonstrate significantly higher mortality rates in hyperglycaemic IS patients (defined as BG level >8 mmol/L, measured within 3 days from stroke onset), compared to normoglycaemic patients. The survival rates did not differ in the glycaemic groups of TIA. In a meta-analysis, admission HG following IS in non-diabetic patients correlates with an increased risk of short-term mortality and poor functional recovery, within 1 month post-stroke [3]. The size of our study population was insufficient to investigate the influence of HG in non-diabetic subjects. It has been reported that the presence of HG before the administration of thrombolysis predicts poorer outcome after re-canalisation [8]. Studies on long-term mortality that report data from both diabetic and non-diabetic subjects, have observed an increased risk for death at 1 year after IS among hyperglycaemic subjects [9]. Previous studies have not evaluated the effect of admission HG on mortality during an observational period as long as 10 years after stroke. In our cohort, mortality rates in hyperglycaemic subjects were significantly higher than in normoglycaemic subjects over 5 years post-stroke. Thereafter, the annual mortality rate in IS remains constantly low, while it steadily rises in normoglycaemic subjects to almost equalise at the tenth year of observation. This could reflect the increasing age of the population. DM was a co-morbidity

in 19% of IS, occurring more often in hyperglycaemic (29%) compared to normoglycaemic subjects (15%). In a previous cohort, DM occurred in 46% of the hyperglycaemic patients (random glucose level ≥8 mmol/L, measured within 24 h from admission) and only in 11% of the normoglycaemic patients [10]. Surprisingly, DM did not significantly influence long-term mortality in IS, whereas it was revealed to be a predictor of death in TIA. Previous studies report male gender, increasing age, DM, HT, previous stroke and cigarette smoking to be significant predictors of long-term survival in TIA [11]. In terms of stroke patients, age, AF, congestive heart failure and early- and late-onset ischaemic heart disease are the most well-known and recognised predictors of mortality at 10 years from symptom onset [12].

The initially predominant hypothesis suggested that stroke-related HG is a stress response that represents an epiphenomenon associated with poorer outcome without having any causal relationship [13]. However, one investigation of glycosylated haemoglobin in stroke patients (IS and primary intracerebral haemorrhage) revealed unrecognised DM or IGT in up to 40% of those with admission glucose levels ≥6.1 mmol/L [14]. Another theory suggests that HG in acute stroke is associated with the induction of an inflammatory state which is possibly reversible with insulin treatment [15]. In thromboembolic stroke patients, decreased in-hospital mortality was associated with normalisation of BG during the first 48 h of hospitalisation [16]. However, studies on the effect of glycaemic control in long-term mortality up to 3 months after IS onset have failed to confirm a significant improvement in the clinical outcome [17, 18]. Our findings highlight the effect of acute HG on IS outcomes and suggest that further larger, population-based studies be performed to confirm this data. There are limitations in our study. It was designed as a retrospective observational, hospital-based study, and the data collection was dependent on the availability and accuracy of the medical records. However, in order to adjust for selection bias, specific inclusion criteria were defined for the collection of our subjects. Also, the 5-year period of screening patients for inclusion accounted for a wide range of observation periods within our sample, which explains the high standard deviation calculated for the mean follow-up time. The lack of routine measurement of glycosylated haemoglobin limited our ability to evaluate the impact of glycaemic control on mortality. The lack of data concerning the causes of death of our deceased subjects limits the possibility to investigate the stroke-related mortality and its association with admission HG. However, this study is based on a large representative for the local population sample of patients, and provides an overview of all-cause mortality during 10 years after an acute cerebrovascular event.

In conclusion, admission glucose level >8 mmol/L after IS is associated with higher mortality up to 5 years after symptom onset, compared to patients with admission normoglycaemia. Further prospective, community-based, cohort studies should be performed to confirm the influence of admission HG on long-term survival after IS.

Key points

- HG (glucose levels >8 mmol/L) at the acute phase of IS is associated with higher mortality rates over 5 years after stroke onset.
- Admission HG was not an independent predictor of long-term mortality, but there was a tendency towards significance. Larger studies could confirm a possible long-term deleterious effect of elevated glucose levels shortly after ischaemic stroke and the role of early insulin treatment on survival.
- Our findings, well in accordance with previous studies on short-term mortality, bring the subject of HG shortly after IS in discussion. Further prospective, community-based cohort studies would be of clinical interest.

Conflicts of interest

None.

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Current patterns of diet in community-dwelling older men and women: results from the Hertfordshire Cohort Study

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Abstract

Background: dietary patterns analysis takes account of the combined effects of foods and may be a more meaningful way of assessing dietary exposure than considering individual nutrients. Little is known about the dietary patterns of older adults in the UK.
Objective: to describe the dietary patterns of a population of community-dwelling older men and women and to examine factors associated with compliance with these patterns.
Setting and Participants: 3,217 men and women aged 59–73 years who were participants in the Hertfordshire Cohort Study.
Methods: diet was assessed using an administered food frequency questionnaire; dietary patterns were identified using principal component analysis.
Results: two dietary patterns were identified. The first was characterised by high consumption of fruit, vegetables, oily fish and wholemeal cereals ('prudent' pattern); the second was characterised by high consumption of vegetables, processed and red meat, fish and puddings ('traditional' pattern). High 'prudent' diet scores were more common in women, in men and women in non-manual classes and in non-smokers (all $P < 0.05$), whilst high 'traditional' diet scores were more common in men, in men and women who had partners and were associated with higher alcohol consumption (all $P < 0.05$).
Conclusions: we have described large variations in food consumption and nutrient intake amongst older adults that are likely to have implications for future health. The specific socio-demographic correlates of the dietary patterns provide insights into the contexts within which good and poor diets exist, and may help in the identification of opportunities for dietary intervention.

Keywords: *dietary patterns, older adults, diet, elderly*