Admission Hyperglycemia Predicts a Worse Outcome in Stroke Patients Treated With Intravenous Thrombolysis

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OBJECTIVE — Admission hyperglycemia has been associated with worse outcomes in ischemic stroke. We hypothesized that hyperglycemia (glucose >8.0 mmol/l) in the hyperacute phase would be independently associated with increased mortality, symptomatic intracerebral hemorrhage (SICH), and poor functional status at 90 days in stroke patients treated with intravenous tissue plasminogen activator (IV-tPA).

RESEARCH DESIGN AND METHODS — Using data from the prospective, multicenter Canadian Alteplase for Stroke Effectiveness Study (CASES), the association between admission glucose >8.0 mmol/l and mortality, SICH, and poor functional status at 90 days (modified Rankin Scale >1) was examined. Similar analyses examining glucose as a continuous measure were conducted.

RESULTS — Of 1,098 patients, 296 (27%) had admission hyperglycemia, including 18% of those without diabetes and 70% of those with diabetes. After multivariable logistic regression, admission hyperglycemia was found to be independently associated with increased risk of death (adjusted risk ratio 1.5 [95% CI 1.2–1.9]), SICH (1.69 [0.95–3.00]), and a decreased probability of a favorable outcome at 90 days (0.7 [0.5–0.9]). An incremental risk of death and SICH and unfavorable 90-day outcomes was observed with increasing admission glucose. This observation held true for patients with and without diabetes.

CONCLUSIONS — In this cohort of IV-tPA–treated stroke patients, admission hyperglycemia was independently associated with increased risk of death, SICH, and poor functional status at 90 days. Treatment trials continue to be urgently needed to determine whether this is a modifiable risk factor for poor outcome.

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Admission hyperglycemia has been associated with a worse functional outcome after ischemic stroke (1–3). Poor functional outcomes and increased mortality have been described in nonthrombolyzed cohorts, and increased rates of intracerebral hemorrhage (ICH) have been found in the few studies in which patients treated with intravenous tissue plasminogen activator (IV-tPA) were studied exclusively (4–6). Baseline hyperglycemia is found more commonly in patients with preexisting diabetes but is also present in a significant proportion of nondiabetic patients (1). A causal relationship between elevated glucose and worse outcomes has not yet been proven, but current guidelines suggest that excessive hyperglycemia be treated in acute stroke patients (7). Trials of insulin therapy to treat hyperglycemia in acute stroke are ongoing (Glucose Regulation in Acute Stroke Patients [GRASP] trial), and two smaller studies showing equivocal results have been published (8,9).

The bulk of previous studies exploring the role of hyperglycemia in stroke have included only nonthrombolyzed patients. Glucose values were measured beyond the hyperacute (≤3 h) phase, and in several of these studies, ischemic and hemorrhagic strokes were pooled in the analyses (1–3,10). The few studies of admission glucose in tPA-treated ischemic stroke patients have all been relatively small (the largest included 748 patients) (4–6,11–15); some were retrospective (5,14), examined only ICH (5) or short-term (<30 days) outcomes (12,14,15), or included patients treated with IV-tPA beyond 3 h (6,14) or with intra-arterial tPA (11). We sought to determine whether, in a large national cohort of stroke patients treated with standard protocol IV-tPA, elevated admission glucose was associated with worse outcomes, particularly disability, death, and symptomatic ICH (SICH).

RESEARCH DESIGN AND METHODS

— Data prospectively collected in the Canadian Alteplase for Stroke Effectiveness Study (CASES) were analyzed (16). This was a national prospective cohort study that led to the full approval of IV-tPA for acute ischemic stroke in Canada. Sixty sites across the country participated over a period of 2.5 years and, where relevant, each center obtained institutional ethics approval for data collection. If patients were incapacitated by their stroke, next of kin provided informed consent. Patients were treated at the discretion of the site neurologist according to Canadian guidelines for intravenous thrombolytic treatment in acute stroke (17).

Baseline demographic data were obtained as were pretreatment basic blood tests and data regarding timing of drug administration and stroke subtype as determined by the site investigator using the Oxfordshire Community Stroke Project classification. Baseline glucose was determined before IV-tPA administration, either by laboratory blood testing or from

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capillary blood. The particular method used was determined by the site's own usual practice and was not specifically recorded. The severity of the baseline neurological deficit was assessed with the National Institutes of Health Stroke Scale (NIHSS) before treatment. The NIHSS is a validated 11-domain systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit, such that a higher score corresponds to a more severe deficit (mild 0–15, severe >15, and maximum 42). The outcome was measured using the 7-point modified Rankin Scale (mRS) at 90 days by clinicians who were not necessarily blinded to patients' baseline glucose values. A favorable outcome was defined as an mRS of 0–1.

All patients underwent a follow-up head computed tomography (CT) scan at 24–48 h. Baseline and follow-up CT scans were centrally reviewed by a stroke neurologist and neuroradiologist blinded to clinical information, and the Alberta Stroke Program Early CT Score (ASPECTS) was applied. ASPECTS is a validated 10-point score assessing the extent of infarction in strokes of the middle cerebral artery using noncontrast CT. A lower score suggests a more extensive area of infarction (minimum score 0) (18). SICH was defined as any hemorrhage documented on a follow-up CT scan that was associated with a decline in neurological status within the first 24 h after thrombolytic treatment as judged by the site investigator, who was not blinded to clinical information. Asymptomatic ICH involved hemorrhage on a follow-up CT scan without associated clinical deterioration.

The definition of admission hyperglycemia was prespecified to be serum glucose >8.0 mmol/l in accordance with other studies (10,13,19). As a primary analysis, patients were dichotomized into those with admission hyperglycemia and those without hyperglycemia and compared with regard to baseline characteristics, rate of SICH, functional outcome at 90 days, and death. A secondary analysis examined the association of these outcomes with admission glucose as a continuous measure.

Statistical analysis

Standard descriptive statistics were used to report the data. Fisher's exact test and Student's *t* test were used to compare the two groups. Both binomial regression and logistic regression were used to develop models for the three outcomes of interest depending upon use. The large sample size provided sufficient power to perform multivariable analysis. For graphical descriptions, multivariable logistic regression was used to plot adjusted curves. For tabular description of risk ratios (RRs), multivariable binomial regression was used to identify predictors of outcome using a log-link function. The final models were all parsimonious models, meaning that variables that were not significant at $P < 0.05$ or variables that showed no evidence of confounding were eliminated from the final models. Models were developed by backwards stepwise elimination beginning with the variables listed in Table 1. Analyses were conducted using STATA 8.2 (StataCorp, College Station, TX).

Table 1—*Baseline patient characteristics*

	Baseline glucose ≤8.0 mmol/l	Baseline glucose >8.0 mmol/l	*P*
n	802	296	
Age (years)	69.7 ± 13.6	71.6 ± 12.0	0.03
Sex (female)	370 (46.4)	125 (42.7)	0.3
Caucasian	699 (92.6)	232 (86.2)	0.003
Vascular risk factors			
Hypertension	369 (48.1)	156 (57.4)	0.009
Diabetes	50 (6.5)	116 (42.6)	<0.001
Atrial fibrillation	160 (20.9)	74 (27.2)	0.035
Dyslipidemia	141 (18.4)	59 (21.7)	0.25
Current cigarette use	130 (16.9)	29 (10.7)	0.014
Ischemic heart disease	165 (21.5)	89 (32.7)	<0.001
Valvular heart disease	30 (3.9)	9 (3.3)	0.85
Congestive heart failure	41 (5.3)	31 (11.4)	0.001
Prior stroke/transient ischemic attack	170 (22.2)	72 (26.5)	0.16
Pretreatment systolic blood pressure (mmHg)	151 ± 21.6	153 ± 21.8	0.18
Pretreatment ASPECTS	8	8	0.64
Baseline NIHSS	14	15	0.14
Protocol violations, all causes	113 (14.1)	39 (13.2)	0.77
Onset-to-treatment time (min)	150 ± 37.2	150 ± 38.9	0.92
Oxfordshire Community Stroke Project stroke subtype			0.8
Total anterior circulation	198 (26.4)	82 (31.1)	
Partial anterior circulation	481 (64.1)	155 (58.7)	
Posterior circulation	22 (2.9)	13 (4.9)	
Lacunar	49 (6.5)	14 (5.3)	

Data are means ± SD, median, or *n* (%). Not all percentages are calculated from the total number of patients because certain clinical variables were not available for all patients.

RESULTS

Baseline characteristics

Of 1,135 patients enrolled in CASES, 1,098 had adequate admission glucose data for inclusion in the current study. Of these patients, median age was 73 years, 45% were women, 96% had an anterior circulation stroke, and 16% had a known prior history of diabetes. A glucose value of 8.0 mmol/l corresponded to the 75th percentile and, overall, 296 (27%) patients had admission hyperglycemia. Hyperglycemia was present in 70% of those with diabetes and 18% of those without diabetes. Hyperglycemic patients were older; were more likely to be non-Caucasian; were more likely to have atrial fibrillation, hypertension, congestive heart failure, coronary artery disease, and known diabetes; and were less likely to be current smokers. The greater prevalence of comorbid illness in the hyperglycemic group is probably explained by older age and the higher proportion of diabetes. There were no differences in sex, stroke subtype, or baseline stroke severity between groups (Table 1). No relationship was observed between baseline serum glucose and baseline NIHSS score.

Table 2—*Outcome at 90 days and SICH in hyperglycemic (baseline glucose >8 mmol/l) and nonhyperglycemic patients with unadjusted and adjusted RRs (after multivariate logistic regression)*

Outcome variable	Baseline glucose ≤8.0 mmol/l	Baseline glucose >8.0 mmol/l	*P*	RR (95% CI) Unadjusted	RR (95% CI) Adjusted
n	802	296			
ICH					
All	213 (26.6)	105 (35.5)	0.007		
Symptomatic	29 (3.6)	20 (6.8)	0.03	1.87 (1.07–3.25)	1.69 (0.95–3.00)
Outcome at 90 days					
Excellent outcome (mRS 0–1)	316 (40)	80 (27.7)	<0.001	0.69 (0.56–0.85)	0.7 (0.5–0.9)
Death from all causes (mRS 6)	148 (18.7)	89 (30.8)	<0.001	1.64 (1.31–2.06)	1.5 (1.2–1.9)

Data are *n* (%). Not all percentages are calculated from the total number of patients because certain outcome variables were not available for all patients.

SICH, 90-day outcome, and death

Rates of ICH, 90-day outcomes, and mortality are shown in Table 2. A total of 49 (4.5%) patients had SICH. Among hyperglycemic patients, this proportion was 6.8% compared with 3.6% for nonhyperglycemic patients ($P = 0.03$), resulting in an unadjusted RR of 1.87 (95% CI 1.07–3.25) for SICH in patients with baseline glucose >8.0 mmol/l (Table 2). Multivariable regression attenuated this relationship somewhat, yielding an adjusted RR of 1.69 (95% CI 0.95–3.00).

Clinical outcomes at 90 days, unadjusted for confounders, are shown in Fig. 1. Only 80 (27.7%) hyperglycemic patients experienced a favorable functional outcome (mRS 0–1) compared with 316 (40%) nonhyperglycemic patients ($P = 0.0002$). The proportion of patients who were dead at the 3 month follow-up was also significantly higher among patients with admission glucose >8.0 mmol/l (30.8 vs. 18.7%, $P < 0.0001$). Unadjusted risk ratios for favorable outcome and death among hyperglycemic patients were 0.69 (95% CI 0.56–0.85) and 1.64 (1.31–2.06), respectively.

After multivariable regression, adjusted risk ratios were 0.7 (95% CI 0.5–0.9) for favorable outcome and 1.5 (1.2–1.9) for death. Multivariable analysis showed that independent predictors of 90-day outcome and death were age, baseline NIHSS, baseline ASPECTS, and admission glucose. Each of these had a comparable magnitude of association with outcome. When dichotomized as age >80 years, baseline NIHSS >15, and ASPECTS >7, unadjusted RRs for favorable functional outcome were 0.64 (95% CI 0.52–0.80), 0.40 (0.32–0.48), and 1.53 (1.26–1.86), respectively. The negative association between admission glucose and functional outcome and death persisted even after exclusion of patients with SICH, a known independent predictor of death and disability after thrombolysis (4,20). These relationships were not different for patients with and without diabetes (no evidence of an interaction effect).

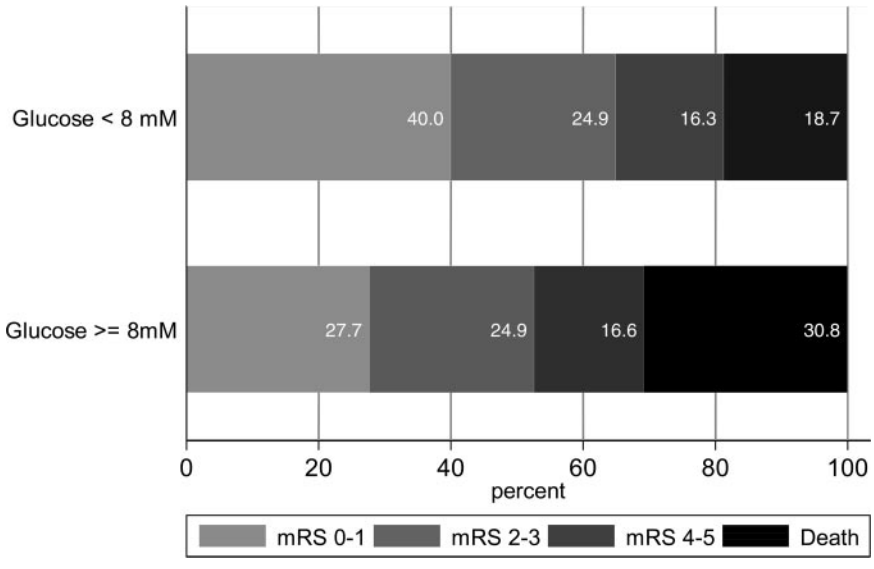

Figure 1— *Patient outcome at the 90-day follow-up by baseline glucose (unadjusted for other predictors of outcome). mRS 0–1, excellent outcome; mRS 2–3, moderate disability; mRS 4–5, severe disability; and mRS 6, dead.*

Effect of stroke subtype and severity

No heterogeneity was found with regard to the association between baseline hyperglycemia and a favorable clinical outcome when analyzed by Oxfordshire Community Stroke Project stroke subtype (χ^2 test, $P = 0.80$) or when mild strokes (NIHSS ≤5) and moderate-to-severe strokes were compared (χ^2 test, $P = 0.29$), suggesting a deleterious effect of hyperglycemia on outcome regardless of stroke subtype or severity.

Admission glucose as a continuous measure

With glucose as a continuous variable, the predicted probability of SICH adjusted for age, atrial fibrillation, onset-to-treatment time, and sex was calculated and represented as a fractional polynomial estimate of best fit (Fig. 2*A*). An increasing probability of SICH was seen with increasing admission glucose values. Similarly, the predicted probability of death at 90 days according to admission glucose, adjusted for age, baseline NIHSS, ASPECTS, onset-to-treatment time, and sex was calculated and represented using a linear least-squares line of best fit (Fig. 2*B*). An increasing risk of death was found with increasing baseline glucose. Finally, the predicted probability of a favorable outcome at 90 days, adjusted for age, baseline NIHSS, ASPECTS, congestive heart failure, atrial fibrillation, and diabetes was determined, yielding an inverse relationship between admission glucose

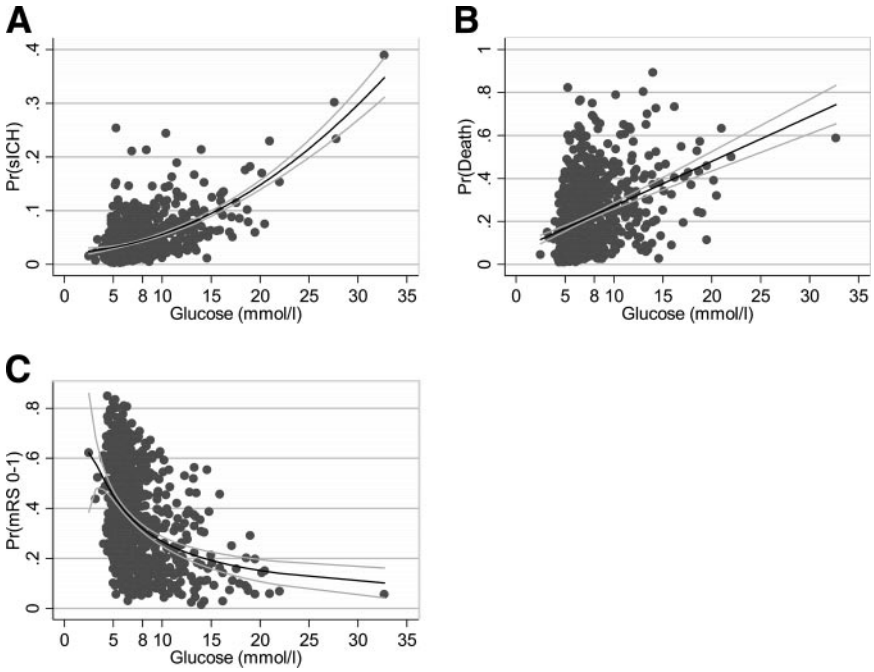

Figure 2— *A: Probability of SICH by baseline glucose level. Quadratic polynomial line of best fit with range and 95% CIs adjusted for age, baseline NIHSS score, sex, onset-to-treatment time, and atrial fibrillation. For each increase of 1 mmol/l of serum glucose, the relative risk of SICH rises by 10%.* B: *Probability of death by baseline glucose level. The line and 95% CIs are based upon a linear regression of predicted probability of death adjusted for age, baseline NIHSS score, sex, onset-to-treatment time, and baseline ASPECTS score. For every 1 mmol/l rise in the baseline serum glucose, the probability of death at 90 days increases by an absolute risk of 2%. C: Relationship between glucose and good outcome. The line and 95% CIs are derived from a fractional polynomial regression of baseline serum glucose and the predicted probability of good outcome adjusted for age, baseline NIHSS score, baseline ASPECTS, sex, and onset-to-treatment time. For every increase of 1 mmol/l of baseline serum glucose, the relative risk of a good outcome falls by 12%.*

levels and the probability of achieving an mRS of 0–1 (Fig. 2*C*). The predicted probability of a favorable outcome was also determined for only those patients with baseline glucose <8 mmol/l. Even among these nonhyperglycemic patients, a linear decline in the probability of a good outcome was seen with increasing glucose levels.

CONCLUSIONS — This study further confirms the relationship between admission hyperglycemia and SICH, death, and poor functional outcome in ischemic stroke patients treated with IV-tPA. Our findings bolster and expand on those of previous studies, the majority of which examined smaller numbers of nonthrombolyzed stroke patients and some of which analyzed hemorrhagic and ischemic strokes together (1–3,10).

Published studies of baseline hyperglycemia in stroke patients treated with thrombolysis have been few, were generally small, and often did not report 3-month outcomes (4,6,12–15). However, all have suggested an increased risk of poor outcome with elevated glucose, despite using different cutoff levels to define hyperglycemia (from 7.7 to 10 mmol/l) (4,6,12–15). One study included 312 tPA-treated patients from the original National Institute of Neurological Disorders and Stroke IV-tPA trial and analyzed these together with 312 placebo-treated patients (4). This study showed that regardless of treatment assignment, as admission glucose level increased, the odds for a favorable outcome progressively decreased and the odds of SICH increased (4). A recent post hoc analysis of 748 patients from the European Cooperative Acute Stroke Study (ECASS-II), a trial of IV-tPA given within 6 h of stroke onset, examined the prognostic value of hyperglycemia at baseline and 24 h (6). Patients were classified into four groups: isolated baseline hyperglycemia, isolated 24-h hyperglycemia, hyperglycemia persisting at both time points, and persistent normoglycemia. Thrombolyzed (n = 384) and nonthrombolyzed (n = 364) patients were analyzed together. Interestingly, isolated baseline hyperglycemia was not found to independently predict poor outcome or ICH. In this study, the strongest predictor of poor outcome, death, and ICH was persistent hyperglycemia at baseline and 24 h, although this observation was only true in patients without known diabetes. The prognostic utility of hyperglycemia exclusively in those patients treated with IV-tPA cannot be determined because this subgroup was not analyzed separately. Two other studies of tPA-treated patients, one with intravenous treatment and the other with intra-arterial treatment, also showed that elevated glucose was an independent predictor of ICH (5,11).

What remains unclear is whether hyperglycemia is merely an epiphenomenon of underlying stroke severity or if it is itself directly harmful to ischemic brain tissue. After adjustment for clinical stroke severity, a dose-response relationship between baseline glucose and unfavorable outcome is still suggested by our results and those of others (1,4,6,10). There is ample animal literature suggesting plausible mechanisms by which glucose may exert a deleterious effect on ischemic brain, including cellular acidosis caused by anaerobic glycolysis, enhanced free radical production, increased blood-brain barrier permeability, impaired mitochondrial function, influx of intracellular Ca^{2+}, and cellular edema (21).

However, noncausal explanations have also been proposed. Baseline hyperglycemia may represent an acute stress response from activation of the hypothalamic-pituitary-adrenal axis causing a rise in cortisol and catecholamines and, therefore, may simply be indicative of underlying stroke severity. Furthermore, it may also be a result of injury or irritation of brain areas involved in glucose regulation, a theory supported by the association of hyperglycemia with strokes involving the insula (22). Finally, hyperglycemia may reflect previously undiagnosed diabetes.

The argument for causality is also further mitigated by the equivocal results of trials targeting aggressive glucose-lowering therapy in the acute phase after stroke (8,9). No evidence to date supports the concept that ensuring strict post-stroke normoglycemia improves outcome. The UK Glucose Insulin in Stroke Trial (GIST-UK) was both stopped early and underpowered but suggested no difference in clinical outcome between pa-

tients randomly assigned to glucose-potassium-insulin infusion to maintain glucose levels at 4–7 mmol/l over the first 24 h and patients given saline without glucose-lowering interventions (9). The lack of benefit may be related to the relatively late initiation of therapy after stroke (median 14 h) and the modest mean reduction in glucose achieved in the treatment arm (0.57 mmol/l).

Our prospective cohort study is the largest yet to report on the effect of admission glucose exclusively in stroke patients treated uniformly with IV-tPA. Our results confirm the notion that poststroke hyperglycemia is a predictor of death, worse functional outcome, and SICH in thrombolyzed patients. This association remains true regardless of stroke subtype or severity and in patients with and without diabetes. We acknowledge that our work has several limitations. First, it is an observational study. Nonetheless, the data were prospectively collected from a large number of representative patients drawn from 60 hospitals across Canada. Second, our results are based on only a single admission glucose value. Contrary to data for acute coronary syndromes arguing that dynamic changes in glucose are not prognostically significant (23), it has recently been suggested that changes in glucose over the first 24 h among stroke patients may provide additional prognostic value (6). However, use of a single baseline glucose value presumably underestimates potential harm, because patients with the highest admission glucose levels would most likely have been treated earlier and more aggressively with glucose-lowering therapies. Also, because thrombolytic treatment is necessarily rapid, a single admission glucose level has greater clinical utility for guiding acute treatment decisions. Third, we did not collect A1C values and so we do not have any measures of chronic dysglycemia. However, in acute coronary syndromes, A1C levels convey little short-term prognostic value with respect to mortality (24). Fourth, the method of blood glucose determination was not uniform, with either capillary blood or laboratory glucose measurements used at different sites. Both methods have been shown to provide comparable results in critically ill patients (25). Fifth, we have no information regarding glycemic management during hospitalization or after discharge. Last, baseline differences between both groups may be potential confounders that cannot be entirely accounted for using statistical adjustments.

Although it remains unclear whether correcting elevated glucose in the acute phase after ischemic stroke is beneficial, it is apparent that admission hyperglycemia rapidly identifies patients at higher risk for poor outcomes in whom glucose levels should be closely monitored.

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