Hyperglycemia Is a Stress Response in Acute Stroke

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To explore further the relation between admission glucose concentration and outcome in stroke, we measured glucose, fructosamine, and glycosylated hemoglobin concentrations on admission in 216 patients seen within 24 hours after the onset of their first stroke. Fructosamine concentration reflects the degree of glycemia in the preceding 4–6 weeks and glycosylated hemoglobin concentration reflects that in the preceding 3 months. Based on clinical, computed tomographic, and necropsy findings, strokes were classified as cortical infarction, lacunar infarction, or intracerebral hemorrhage. Analyses were done including and excluding 47 diabetic patients. No correlation between neurologic outcome as mortality and fructosamine or glycosylated hemoglobin concentration was found. Survival showed a significant correlation with admission glucose concentration only for patients with intracerebral hemorrhage. Our results suggest that hyperglycemia is unlikely to worsen the outcome of acute stroke and that hyperglycemia probably represents either a latent diabetic state or a stress response. (Stroke 1988;19:1359–1364)

In the setting of acute stroke, is hyperglycemia a determinant of poor outcome or does it represent an acute response to stress1 or abnormal glucose tolerance? Glycosylated serum protein (fructosamine) and glycosylated hemoglobin (HbA1) are known indexes of medium- and long-term exposure to blood glucose and have been used to monitor the degree of glycemic control in diabetic patients.2–6 As these measures are stable products not influenced by short-term fluctuations, they are superior to the admission glucose concentration as a clinical indicator of the glucose level at the onset of ischemia. If glucose concentration were an important determinant of ischemic brain injury, then fructosamine and HbA1 concentrations should show a correlation with outcome. We tested this hypothesis in our prospective study of 216 acute stroke patients.

Subjects and Methods

We included all stroke patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, during the 6 months from July to December 1986 in our study, provided they satisfied the following entry criteria: admission within 24 hours after the onset of ictus; blood glucose, fructosamine, and HbA1 concentrations determined immediately upon admission and before the administration of any intravenous fluid; diagnosis of stroke confirmed by computed tomography (CT) or necropsy; exclusion of other causes presenting with a stroke-like syndrome, such as subdural hematoma or epilepsy; and no prior neurologic disability from previous strokes or other diseases. CT was performed as soon as possible after admission and was repeated if the clinical features or the initial scan did not allow accurate classification.

We considered three subtypes of stroke: 1) cortical infarction (CI), ischemic stroke in patients with clinical evidence of cortical deficits and CT or necropsy evidence of recent cortical infarction including patients without cortical deficits in whom CT showed a subcortical lesion of >1.5 cm diameter; 2) lacunar infarction (LI), lacunar syndromes in patients without cortical deficits in whom CT was normal or showed a lucency characteristic of a lacune having a maximal diameter of ≤1.5 cm; 3) intracerebral hemorrhage (H), stroke caused by nontraumatic bleeding, primarily into the brain substance, with or without the presence of blood in the ventricles or the subarachnoid space.

We categorized patients for analysis: Category I included all patients satisfying the entry criteria irrespective of diabetic state and Category II excluded patients with a known history of diabetes mellitus, persistent hyperglycemia during the acute admission requiring insulin or oral hypoglycemic
therapy, or a diabetic oral glucose tolerance test (OGTT) 3–6 months after ictus.

The degree of glycemic control was assessed by fructosamine and HbA\(_1c\) concentrations, which represent the time-averaged values for blood glucose over the preceding 4–6 weeks (for fructosamine) and 3 months (for HbA\(_1c\)). Serum fructosamine was measured by colorimetric assay\(^7,8\) using the Abbott VP automated bichromatic analyzer (Abbott Laboratories Inc., Chicago, Illinois). The between-run coefficient of variation is 3% at 2.5 mmol/l fructosamine. HbA\(_1c\) was electrophoresed on agar gel using the Corning Electrophoresis System and quantified using the Corning M710 fluorimeter/densitometer (Corning Medical, Halstead, UK) with prior removal of the labile fraction by incubation with saponin reagent.\(^9\) The between-run coefficient of variation is 6% at 8% HbA\(_1c\). When HbA\(_1c\) exceeded 12%, the result was checked by affinity chromatography\(^10\) using Pierce prepacked Glyco Gel analytical columns and Pierce reagents (Pierce Chemical Co., Rockford, Illinois). The between-run coefficient of variation is 9%.

Standard 2-hour 75-g OGTTs were performed in all survivors 3–6 months after ictus following an overnight fast. Blood glucose was measured using Abbott hexokinase reagent and the Abbott VP automated bichromatic analyzer.\(^11^\) Results were interpreted using criteria of the World Health Organization\(^12\) to distinguish diabetic from nondiabetic subjects.

Neurologic outcome was assessed by mortality at 1 week, 6 weeks, and 3 months.

Statistical analysis was performed with the aid of the Statistical Package for the Social Sciences (SPSS-X). Data were analyzed using Student’s two-tailed \(t\) test or the \(\chi^2\) test where appropriate. The probability value was adjusted for multiple comparisons.\(^13\)

**Results**

The total number of patients initially admitted was 229, but we excluded 13 from the study because of lack of CT or necropsy confirmation (in six), blood sampling >24 hours after the onset of ictus (in three), intravenous fluid administration before blood sampling (in three), and subdural hematoma (in one). The remaining 216 patients comprise Category I. The stroke subtype was confirmed by CT in 202 patients (93.5%) and by necropsy in the remaining 14 (6.5%). Of the 202 patients, CT was performed within 48 hours after onset of ictus in 61.9%, 3–7 days after onset of ictus in 16.8%, during the second week after onset of ictus in 15.4%, and during the third week after onset of ictus in the remaining 5.9%. CT was repeated 6–8 weeks after the ictus in 26 patients to accurately classify them as to stroke subtype.

Ten CI, 15 LI, and four H patients had a known history of diabetes mellitus. In addition, four CI, three LI, and 11 H patients were found to be diabetic on the basis of either persistent hyperglycemia during the acute admission or the OGTT performed 3–6 months after ictus. We excluded these 47 patients from Category I to form Category II. The demographics and the risk factor distribution for patients in Categories I and II are shown in Table 1.

CI patients had higher admission glucose concentrations than LI patients in both categories, while H patients consistently had the highest admission glucose concentrations irrespective of category. On the other hand, fructosamine and HbA\(_1c\) concentrations and the number of diabetics by history were not different among the three stroke subtypes.

Among Category I patients, there was a significant correlation between any two of glucose, fructosamine, and HbA\(_1c\) concentrations within each stroke subtype (Table 2). However, after exclusion of the diabetic patients, there was a significant correlation only between fructosamine and HbA\(_1c\) concentrations within each stroke subtype, and glucose concentration no longer showed any correlation with either fructosamine or HbA\(_1c\) concentration.

Table 1 shows the neurologic outcome for patients in both categories. Mortality was highest for H patients, especially at 1 week. CI patients had significantly higher mortality than LI patients. As only two LI patients died, no comparison of glycemic parameters in relation to mortality was made within this stroke subtype. CI and LI patients were combined into an ischemic stroke group for further analysis.

A comparison of glucose concentration by stroke subtype in relation to mortality shows that among patients with ischemic strokes, there was no difference in glucose concentrations between those who survived and those who died in either category (Figure 1). For H patients, admission glucose concentration was significantly higher in those who died than in those who survived in both categories.

Considering fructosamine concentration in relation to mortality, among patients with ischemic strokes, survivors generally had a higher concentration, although the difference did not reach significance in either category (Figure 2). For H patients, there was no difference in fructosamine concentrations between those who survived and those who died in either category.

While the trend among patients with ischemic strokes in Category I was for survivors to have higher HbA\(_1c\) concentrations, there was no significant difference between those who survived and those who died (Figure 3). Among Category II patients with ischemic strokes, survivors generally had lower HbA\(_1c\) concentrations although, again, the difference did not reach significance at any time after ictus. There was no correlation between HbA\(_1c\) concentration and mortality among the H patients in either category.

**Discussion**

Myers and Yamaguchi\(^14\) first noted the harmful effects of hyperglycemia in cerebral ischemia.
Administration of glucose to monkeys just before cardiac arrest markedly augmented the severity of brain injury. Their study was followed by further experimental evidence\textsuperscript{15–18} that glucose exerts a deleterious effect in cerebral ischemia, the mechanism of which is postulated to be severe tissue lactic acidosis.\textsuperscript{16,19} A number of clinical studies\textsuperscript{20–23} have shown a correlation between admission glucose levels in patients with acute cerebral infarction and neurologic outcome, consonant with the experimental studies, although there have been some reports to the contrary.\textsuperscript{1,24–26} A factor contributing to these conflicting results is the lumping of patients with CI and LI.\textsuperscript{26}

The major difficulty in clinical studies lies in interpreting the admission glucose concentration. This value may be influenced by a number of factors, including the stress of an acute medical illness,\textsuperscript{27,28} the interval between onset of the stroke and blood sampling, and any underlying illness, especially a latent diabetic state.\textsuperscript{29} To circumvent these difficulties, we limited our cohort to patients seen within 24 hours after the onset of ictus and performed OGTTs on all survivors in the chronic phase to search for latent diabetes mellitus. Most importantly, we examined fructosamine and HbA\textsubscript{1c} concentrations, which reflect the degree of glycemia before the onset of the stroke, to overcome the confounding effect of acute stress on the admission glucose concentration.

Although correlation between fructosamine concentration and stroke outcome has not been studied, the prognostic value of HbA\textsubscript{1c} concentration in stroke has been described.\textsuperscript{30–32} Oppenheimer et al\textsuperscript{\textsuperscript{10}} employed random HbA\textsubscript{1c} concentrations and history to categorize diabetic status in 100 patients and...
concluded that premorbid abnormal glucose tolerance was the major determinant of the hyperglycemic response to stroke. Cox and Lorains,31 in a prospective study of 109 patients, found that hyperglycemia with normal HbA1c concentration, which represents “stress” hyperglycemia, was associated with a poor prognosis. Neither study directly correlated HbA1c concentration with mortality, analyzed nondiabetics, or characterized the subtype of stroke.

We correlated fructosamine and HbA1c concentrations with outcome as stroke mortality, not only for all patients entered into our study, but also for a nondiabetic category that showed the same results. Among H patients (who had the highest mortality among the three stroke subtypes), admission glucose concentration best predicted outcome. For the group of ischemic strokes, CI patients had significantly higher mortality than LI patients and higher admission glucose concentrations, which reached significance in Category II. Fructosamine and HbA1c concentrations showed no correlation with outcome in any stroke subtype. The lack of correlation between these measures and outcome favors the argument that a high admission glucose concentration is the effect rather than the cause of a stroke.

Debate continues on whether a cyclic process exists in which stroke-induced stress causes hyperglycemia, which may in turn further extend the cerebral infarct. Some investigators have suggested that blood glucose levels should be maintained in the near-normal range in any patient with impending or evolving cerebral ischemia.20 Our data question the wisdom of such vigorous attempts, although avoiding glucose-containing infusions in the immediate treatment is justified. While we failed to confirm a causal role for hyperglycemia in stroke outcome, the admission glucose level still has prog-
outcome may shed further light on this important

rhage (H) subtypes for Categories I and II. Number of

and lacunar infarction (LI), and intracerebral hemor-

concentration in relation to mortality at 1 week, 6 weeks,

Bar graphs of glycosylated hemoglobin (HbA

Diagnostic importance. Noting the actual interval

between the onset of stroke and blood sampling for

glucose determination and correlating these with

outcome may shed further light on this important

clinical question.

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References

1. Melamed E: Reactive hyperglycemia in patients with acute


2. Service FJ, O'Brien PC, Rizza RA: Measurements of glu-


3. Bunn HF, Gabbay KH, Gallop PM: The glycosylation of

hemoglobin: Relevance to diabetes mellitus. Science 1978;

200:21-27


approach to the estimation of serum glycosylated protein.


5. Yue DK, Morris K, McLennan S, Turtle JR: Glycosylation

of plasma protein and its relation to glycosylated hemoglobin


6. Health and Public Policy Committee, American College

of Physicians: Glycosylated hemoglobin assays in the manage-

ment and diagnosis of diabetes mellitus. Ann Intern Med

1984;101:710-713

7. Mayer TK, Freedman ZR: Protein glycosylation in diabetes

mellitus: A review of laboratory measurements and of their


8. Baker JR, Metcalf PA, Johnson PN, Newman D, Rietz P:

Use of protein-based standards in the automated colorimet-

ric determinations of fructosamine in serum. Clin Chem

1985;31:1550-1554

9. Menard LA, Dempsey ME, Blankstein LA, Stastny M: A

simple electrophoretic method for the quantitative determi-

nation of glycosylated hemoglobin (HbA\(_{\text{1c}}\)) (abstract). Clin

Chem 1980;26:1057

10. Mallia AK, Hermanson GT, Blankenstein LA, Fleischer

PK: Preparation and use of a boronic acid affinity support for

separation and quantitation of glycosylated hemoglobin.

Anal Lett 1981;14:649-661

11. Package insert 95-8838-FO. Chicago, Abbott Laboratories

Inc, 1981

12. WHO Expert Committee on Diabetes Mellitus: Second

report. WHO Tech Rep Ser 1980;646:1-80

13. Cupples LA, Heeren T, Schatzkin A, Colton T: Multiple

testing of hypotheses in comparing two groups. Ann Intern

Med 1984;100:122-129

14. Myers RE, Yamanouchi S: Nervous system effects of cardiac


15. Siemkowicz E, Hansen AJ: Clinical restitution following

cerebral ischemia in hypo-, normo- and hyperglycemic rats.

Acta Neurol Scand 1979;58:1-8

16. Rehncrona S, Rosén I, Siegö BK: Excessive cellular acidosis:

An important mechanism of neuronal damage in the brain?


17. Welsh FA, Ginsberg MD, Rieder W, Budd WW: Deleterious

effect of glucose pretreatment on recovery from diffuse

cerebral ischemia in the cat. II. Regional metabolic levels.

Stroke 1980;11:355-363

18. Pulsinelli WA, Waldman S, Rawlinson D, Plum F: Moderate

hyperglycemia augments ischemic brain damage: A neuro-

pathologic study in the rat. Neurology 1982;32:1239-1246

19. Plum F: What causes infarction in ischemic brain?: The


20. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F:

Increased damage after ischemic stroke in patients with

hyperglycemia with or without established diabetes mellitus.


WA, Plum F: Clinical predictors of recovery from ischemic

stroke, in Reivich M, Hurtig HI (eds): Cerebrovascular Dis-


22. Mohr JP, Rubenstein LV, Tatemichi TK, Nichols FT, Caplan

LR, Hier DB, Kase CS, Price TR, Wolf PA: Blood sugar and

acute stroke: The NINCDS Pilot Stroke Data Bank (abstract).

Stroke 1985;15:143

23. Berger L, Hakim AM: The association of hyperglycemia with

cerebral edema in stroke. Stroke 1986;17:865-871

24. Longstreth WT Jr, Diehr P, Cobb LA, Hanson RW, Blair

AD: Neurologic outcome and blood glucose levels during

discontinuation of hospital cardiopulmonary resuscitation.

Neurology 1986;36:1186-1191


of admission blood glucose in predicting outcome of

acute cerebral infarction (abstract). Stroke 1987;18:297


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