Relationship Between Admission Hyperglycemia and Neurologic Outcome of Severely Brain-Injured Patients

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Severe head injury is associated with a stress response that includes hyperglycemia, which has been shown to worsen outcome before or during cerebral ischemia. To better define the relationship between human head injury and hyperglycemia, glucose levels were followed in 59 consecutive brain-injured patients from hospital admission up to 18 days after injury. The patients who had the highest peak admission 24-hour serum glucose levels had the worse 18-day neurologic outcome ($p = 0.01$). Patients with peak 24-hour admission glucose levels greater than 200 mg/dL had a two-unit increase in Glasgow Coma Scale score while patients with admission peak 24-hour serum glucose levels less than or equal to 200 mg/dL had a four-unit increase in Glasgow Coma Scale score during the 18-day study period ($p = 0.04$). There was a significant relationship between 3-month and 1-year outcome and peak admission 24-hour serum glucose level ($p = 0.02$ and $p = 0.02$, respectively). Those patients with admission peak 24-hour serum glucose levels less than or equal to 200 mg/dL had a greater percentage of favorable outcome at 18 days, 3 months, and 1 year than those with admission peak 24-hour glucose levels greater than 200 mg/dL ($p = 0.0007$, $p = 0.03$, and $p = 0.005$, respectively). A significant relationship between admission peak 24-hour Glasgow Coma Scale score and 18-day, 3-month, and 1-year outcomes was found ($p = 0.0001$, $p = 0.0002$, and $p = 0.0002$, respectively). Patients with mean admission peak 24-hour Glasgow Coma Scale scores of 3.5, 6, and 10 had mean admission 24-hour peak serum glucose levels of 252 ± 23.5, 219.1 ± 19, and 185.8 ± 21, respectively ($p = 0.05$). These relationships were not significantly altered when confounding variables such as the amount of glucose given over the initial 24-hour postinjury period, the presence of diabetes or multiple injuries, and whether patients were given steroids, dilantin, or insulin were statistically incorporated. These data suggest that admission hyperglycemia is a frequent component of the stress response to head injury, a significant indicator of severity of injury, and a significant predictor of outcome from head injury.

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SEVERE HEAD INJURY is associated with an acute sympathoadenomedullary response characterized by increased blood levels of norepinephrine, epinephrine, and dopamine.[1-3] The levels of circulating catecholamines are inversely related to the severity of brain injury.[1] Rosner et al.[3] showed that hyperglycemia occurred within minutes of experimental head injury in cats. In this animal model, hyperglycemia was related to severity of injury and was thought to be caused by catecholamine release. The relationship between human head injury and blood glucose levels has not been determined. We report a significant relationship between hyperglycemia and severity of human brain injury.

Methods

Fifty-nine consecutive brain-injured patients were studied from hospital admission to 18 days after injury. All had peak 24-hour Glasgow Coma Scale (GCS) scores between 4 and 10 during the first 24 hours of hospital admission. The ratio of male patients to female patients was five to one, and the mean age of the patients was 31.4 years. The mean admission peak 24-hour GCS score was 6.9. The primary injury in all patients was to the brain, and 28% of patients had extracranial injuries including rib or long-bone fractures, pneumothoraces, or abdominal injuries. Forty-eight per cent of patients had closed head injuries, 21% had gunshot wounds, 9% had depressed skull fractures with brain contusions, and 22% suffered hematomas.

The amount of glucose infused during the first 24 hours after injury was ascertained. Serum glucose levels were obtained on admission to the emergency unit, three times per day while in the intensive care unit, and daily while

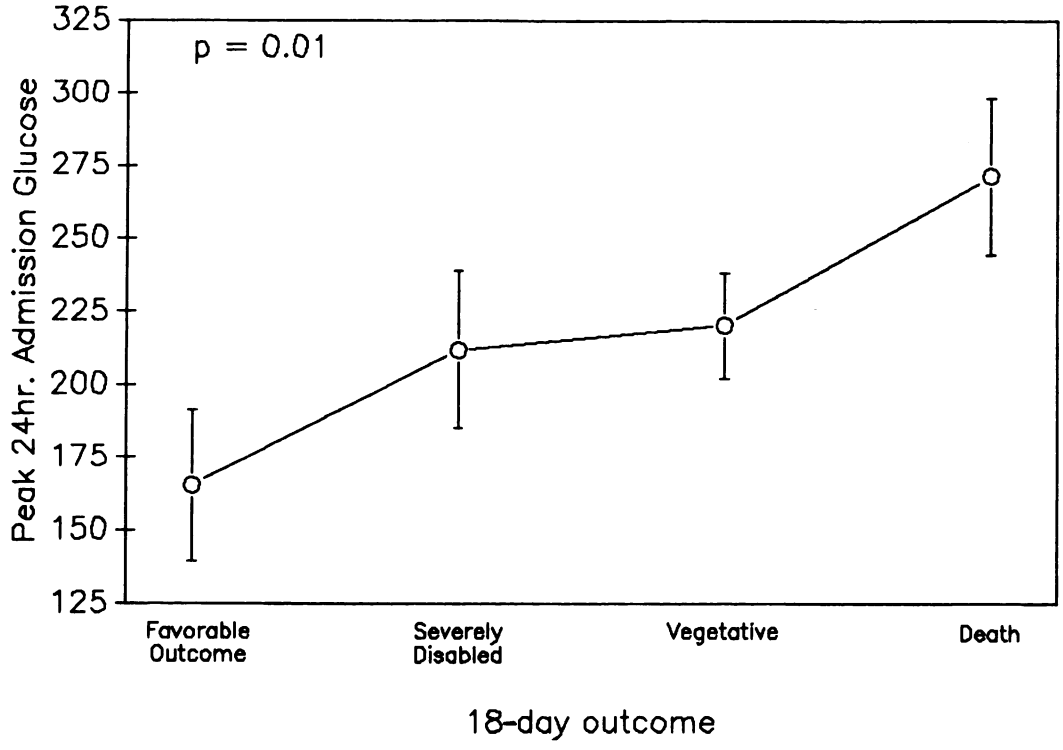

FIG. 1. Peak 24-hour admission serum glucose level *versus* Glasgow Outcome Scale score 18 days after injury in 59 severely head-injured patients. All values are mean ± SEM.

in the hospital ward. Control of serum glucose levels greater than 200 mg/dL was attempted by treatment with insulin and withholding of intravenous dextrose solutions. No patients received corticosteroids after admission to our unit. Twenty per cent of patients were given corticosteroids once for cerebral edema by the referring physician. Preinjury presence of diabetes was noted, as was the use of Dilantin (Parke-Davis, Division of Warner-Lambert, Co., Morris Plains, NJ).

Daily peak serum glucose levels were obtained for the first seven days after injury. Daily peak GCS score was determined for the first 18 days after injury. Neurologic outcome was assessed by the Glasgow Outcome Scale (GOS) at 18 days, 3 months, 6 months, and 1 year after injury. Neurologic outcome at 18 days, 3 months, and 1 year, and admission GCS were evaluated in relationship to peak daily serum glucose levels.

Statistics

Comparison of serum glucose levels by outcome was made by one-way analysis of variance (ANOVA). Significance reflects a test for linear effect when outcome classes are equally spaced or when using the midpoint of classes, and adjustment for 24-hour glucose infusion was by covariate analysis of variance. The outcome classes are death, vegetative, severely disabled, and good recovery (moderately disabled and favorable outcome). Change in GCS from days 1 to 18 for patients with high and low admission glucose was assessed by repeated measures of ANOVA, while adjustment for 24-hour glucose infusion was by covariate analysis of variance. Percentages of favorable outcome by high or low admission glucose were evaluated by the chi square test. The relationship between GCS, glucose level, and outcome was assessed by a correlation coefficient, while a partial correlation coefficient was used to evaluate the independence of these relationships, as well as to adjust for 24-hour glucose influence. The means reported in Table 1 are least square means that reflect the adjustment for 24-hour glucose infusion.

Results

Forty-eight per cent of the patients had peak admission glucose levels greater than 200 mg/dL, 26% had levels between 160 and 200 mg/dL, and 26% were less than 160 mg/dL. Only four patients had peak 24-hour admission serum glucose levels less than 120 mg/dL. The patients who had the highest peak admission 24-hour serum glucose levels had the worst 18-day neurologic outcomes ($p = 0.01$). Patients with 18-day outcomes of death, vegetative, severe disability, and moderate or good recovery had mean 24-hour admission peak blood glucose levels of 271.6 ± 27, 220.4 ± 18, 212.1 ± 27, and 165.5 ± 26, respectively (Fig. 1). Patients with peak 24-hour serum glucose levels greater than 200 mg/dL had a two-unit increase in GCS score during the 18-day study period, while patients with admission peak 24-hour serum glucose levels

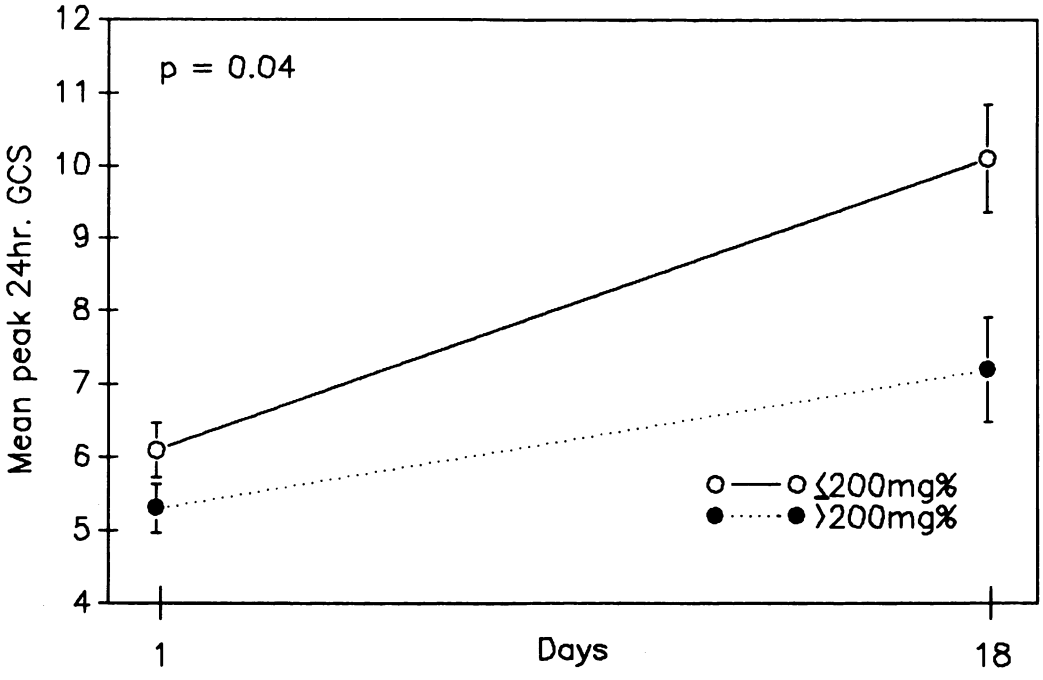

FIG. 2. Glasgow Coma Scale score one day and 18 days after injury in patients with serum admission peak 24-hour glucose levels less than or equal to or greater than 200 mg%. All values are mean ± SEM.

less than 200 mg/dL had a four-unit increase in GCS score during the 18-day study period ($p = 0.04$; Fig. 2). There was a significant linear trend for 3-month and 1-year outcomes and admission peak 24-hour serum glucose level ($p = 0.02$, $p = 0.02$, respectively; Figs. 3 and 4). Patients with admission peak serum glucose levels less than or equal to 200 mg/dL had a greater percentage of favorable outcomes at 18 days, 3 months, and 1 year than those with admission peak 24-hour glucose levels greater than 200 mg/dL ($p = 0.0007$, $p = 0.03$, and $p = 0.005$, respectively; Fig. 5). There was a significant relationship between admission peak 24-hour GCS score and 18-day,

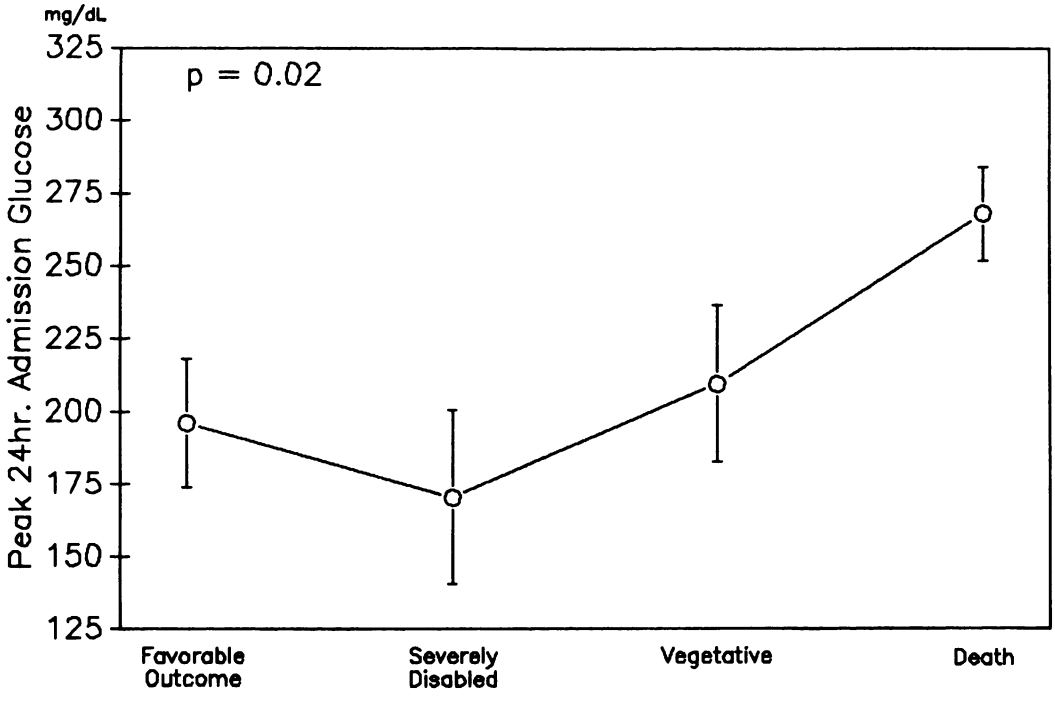

FIG. 3. Peak 24-hour admission serum glucose level *versus* Glasgow Outcome Scale score 3 months after injury in 59 severely head-injured patients. All values are mean ± SEM.

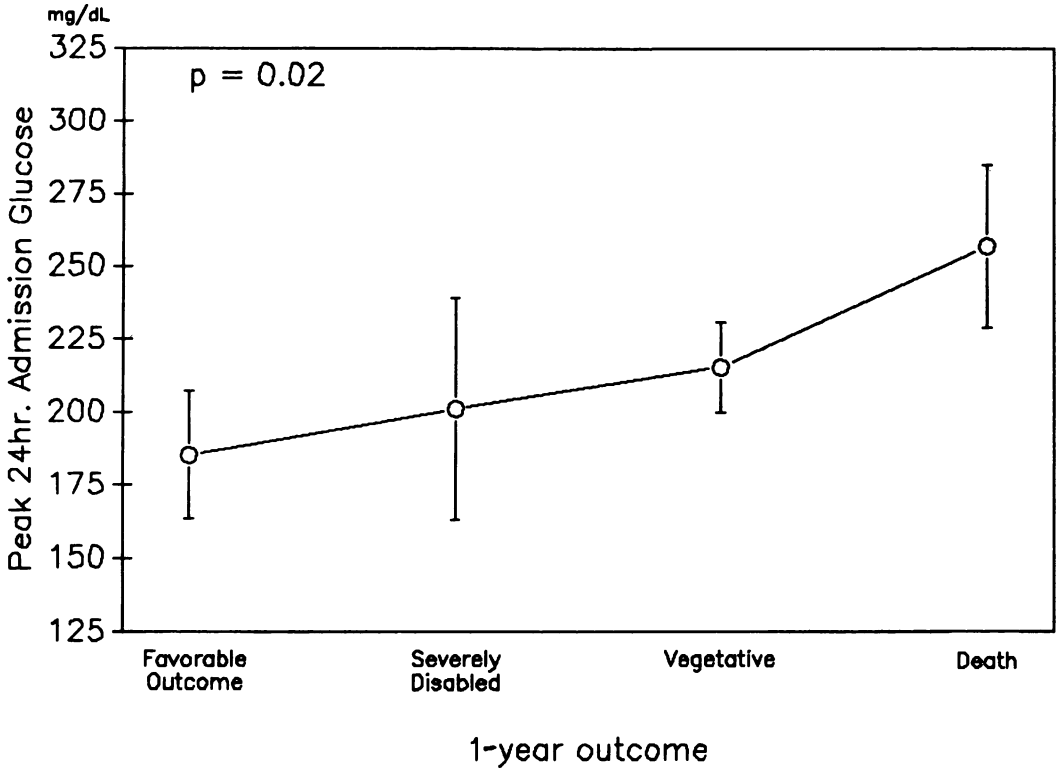

FIG. 4. Peak 24-hour admission serum glucose level *versus* serum Glasgow Outcome Scale score 1 year after injury in 59 severely head-injured patients. All values are mean ± SEM.

3-month, and 1-year outcomes ($p = 0.0001$, $p = 0.0002$, $p = 0.0002$, respectively). Although admission glucose levels were also significantly related to 18-day, 3-month, and 1-year outcomes, this relationship tended to disappear when adjustment was made for admission peak 24-hour GCS. Admission peak 24-hour glucose levels were significantly related to admission peak 24-hour GCS score ($p = 0.05$). Patients with admission mean peak 24-hour GCS scores of 3.5, 6, and 10 had mean admission 24-hour peak serum glucose levels of 252 ± 23.5, 219.1 ± 19, and 185.8 ± 21, respectively (Fig. 6). Statistical inclusion of the amount of glucose administered to patients within the first 24 hours did not significantly affect the results (Tables 1 to 3). The percentages were not remarkably altered for

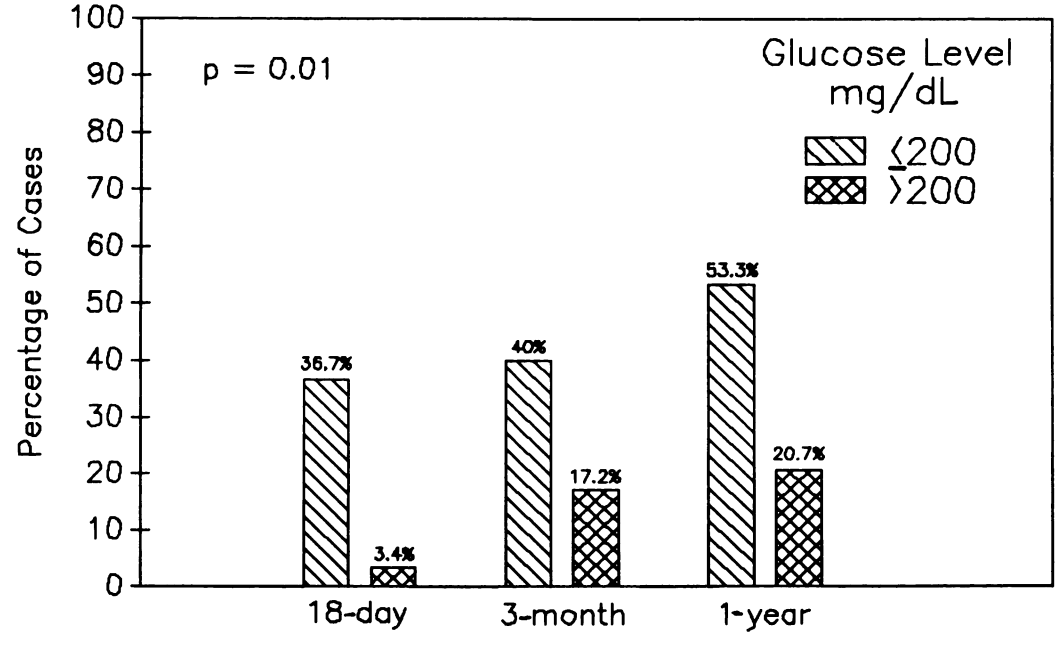

FIG. 5. Percentage of patients with favorable outcomes 18 days, 3 months, and 1 year after injury in patients with peak 24-hour admission serum glucose levels less than or greater than 200 mg%. All values are percentages.

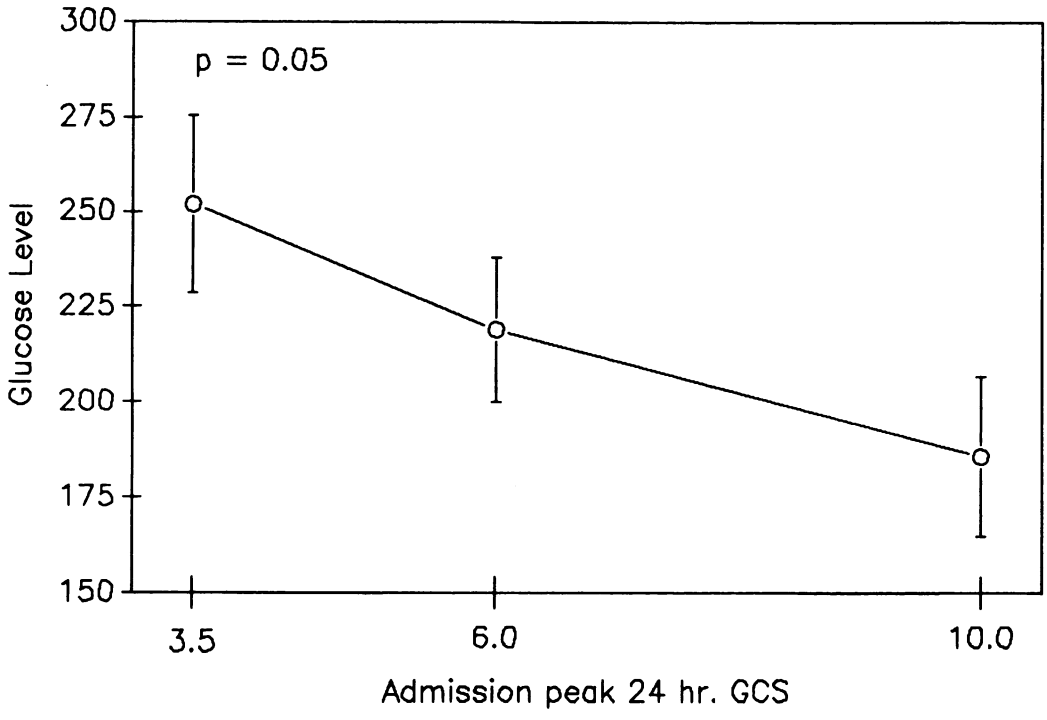

FIG. 6. Peak admission 24-hour serum glucose level *versus* peak admission 24-hour Glasgow Coma Scale score in 59 severely head-injured patients. All values are mean ± SEM.

patients given or not given Decadron (Merck Sharp and Dohme, West Point, PA), with or without systemic injuries, given or not given insulin, with or without diabetes, and given or not given dilantin, with the exception of patients on Decadron (1-year outcome) (Table 4). No relationship between serum glucose levels and outcome could be found after the first day after injury.

Discussion

This study showed that admission peak 24-hour GCS scores and admission peak 24-hour serum glucose levels are significantly related, despite the presence of confounding variables such as glucose, steroid, dilantin, or insulin administration and the presence of multisystem injury or diabetes. Hyperglycemia is a component of the stress response to injury.[4] Blood glucose levels have been shown by Rosner[3] to be elevated in the cat experimental head injury model. Rosner et al.[3] speculated that hyperglycemia and increased blood catecholamines were causally related. Catecholamines and glucagon stimulate the breakdown of glycogen stored in the liver into glucose.[4,5] Bessey et al.[6] have shown in normal humans that a triple hormone infusion (glucagon, catecholamines, and cortisol) causes hyperglycemia similar to that observed in mild to moderate stress. A single hormone infusion of either catecholamines, glucagon, or cortisol alone did not cause hyperglycemia. This finding suggests a synergistic hormonal effect after injury.

Catecholamines increase glucagon secretion and inhibit insulin secretion after injury and stress.[5] The mechanism of sympathetic system activation has not been resolved. Specific focal hypothalamic and/or brain stem injury and diffuse white matter injury may be responsible.[7] Alternately the release of interleukin-1, the cytokine mediating the acute phase response, could play a role.[8]

There is a considerable body of evidence from human and animal studies to show that hyperglycemia increases

TABLE 1. *Mean (±SEM) Admission 24-Hour GCS* Versus *Admission Peak 24-Hour Glucose Level*

	Linear Effect	
Admission Peak 24-Hour GCS	Mean (±SEM) Admission Peak 24-Hour Glucose Level (mg/dL)	Column II Parameters Adjusted for 24-Hour Glucose Infusion (mg/dL)
3–4 (3.5)	252.0 (±23.94)	236.5 (±21.76)
5–7 (6)	219.1 (±19.15)	203.8 (±21.17)
>8	184.1 (±22.57)	191.6 (±25.06)

p value = 0.05; p = 0.21.

TABLE 2. *Outcome Class* Versus *GCS Class*

	p Values		
	18-Day	3-Month	1-Year
Unadjusted	0.01	0.02	0.02
Adjusted for 24-hour glucose infusion	0.03	0.08	0.05

TABLE 3. *Partial Correlations and Value for GOS* Versus *GCS*

Neurologic Outcome	Partial Correlation and p Value for GOS *Versus* GCS	Column II Parameters Adjusted for 24-hour Glucose Infusion
18-day	−0.24 (0.07)	−0.22 (0.12)
3-month	−0.20 (0.13)	−0.17 (0.23)
1-year	−0.21 (0.11)	−0.17 (0.22)

the morbidity and mortality produced by cerebral ischemic insults such as cardiac arrest and stroke.[9,10] During normal aerobic metabolism, glucose is converted into pyruvate.[11] Pyruvate then enters the Kreb's cycle as a source of energy (ATP). When the supply of oxygen is limited, pyruvate is alternatively reduced to lactate. Increased levels of lactate and low pH damages brain cells.[12] The mechanisms for increased ischemic damage to brain in the presence of hyperglycemia are (1) anaerobic metabolism in which glucose is converted to lactate rather than pyruvate, and (2) increased levels of glucose, available for lactate production, that lead to secondary neuronal damage due to lactate accumulation.

Other investigators have observed relationships between degree of hyperglycemia and neurological outcome. D'Alecy et al.[13] demonstrated that dogs randomly infused with 5% dextrose in lactated Ringer's solution that underwent subsequent cardiac arrest had significantly increased neurologic deficits 24 hours after injury compared to a control group infused with lactated Ringer's solution. Serum hyperglycemia was evident in the group with the worst neurologic outcome. Longstreth et al.[14] showed a relationship between blood glucose and neurologic recovery after cardiac arrest in 430 patients. Mean blood glucose at the time of hospital admission was higher in the 154 patients who never awakened than in 276 patients who did awaken ($p < 0.05$). Among the latter group, 90 patients with persistent neurologic deficits had higher serum glucose levels than those without persistent deficits ($p < 0.02$). Pulsinelli et al.[15] found that patients with ischemic stroke who had blood glucose levels greater than 120 mg/dL at hospital admission had a significantly worse neurologic outcome than those with blood glucose levels less than 120 mg/dL. Less than one half (43%) of those with blood glucose levels exceeding 120 mg/dL were able to return to gainful employment, whereas three fourths (76%) of those with low blood sugar were able to do so. Pulsinelli et al.[16] found that increasing blood glucose levels, two- or threefold, in rats subjected to four-vessel occlusion significantly worsened ischemic brain damage. Pentelenyi et al.[17] correlated blood glucose and serum insulin levels with level of consciousness in head-injured patients. Merguerian et al.[18] described an association between hyperglycemia (glucose > 270 mg%) and a high mortality rate in head-injured patients.

TABLE 4. *Admission Peak 24-Hour Glucose* Versus *Outcome (Favorable, Unfavorable)**

Group	% Favorable (18 days) Glucose Level >200 mg%	% Favorable (18 days) Glucose Level ≤200 mg%
Overall	1 (3.4%)	11 (36.7%)
Decadron		
Yes (n = 18)	8.0	50.0
No (n = 41)	0.0	36.0
Systemic injury		
Yes (n = 7)	0.0	20.0
No (n = 52)	3.8	42.3
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	3.7	39.3
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	3.7	40.0
Dilantin		
Yes (n = 20)	0.0	54.6
No (n = 39)	5.3	30.0

Group	% Favorable (3 Months) Glucose > 200 mg%	% Favorable (3 Months) Glucose ≤ 200 mg%
Overall	5 (17.2%)	12 (40.0%)
Decadron		
Yes (n = 18)	16.7	66.7
No (n = 41)	18.8	36.0
Systemic injury		
Yes (n = 7)	0.0	20.0
No (n = 52)	19.2	46.2
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	18.5	42.9
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	18.5	43.3
Dilantin		
Yes (n = 20)	11.1	54.6
No (n = 39)	21.0	35.0

Group	% Favorable (1 year) Glucose > 200 mg%	% Favorable (1 year) Glucose ≤ 200 mg%
Overall	6 (20.7%)	16 (53.3%)
Decadron		
Yes (n = 18)	16.7	100.0
No (n = 41)	25.0	44.0
Systemic injury		
Yes (n = 7)	0.0	40.0
No (n = 52)	23.1	57.7
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	22.2	57.1
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	22.2	56.7
Dilantin		
Yes (n = 20)	11.1	54.6
No (n = 39)	26.3	55.0

* Favorable outcome equals good recovery and moderate disability. Unfavorable outcome equals severe disability, vegetative state, and death.

Increased brain lactate levels have been associated with hyperglycemia-induced damage. Welsh found that ischemia of 15 to 30 minutes duration caused a greater accumulation of lactic acid in the brains of glucose-infused animals than in those not infused with glucose, as well as a reduction in cortex and white matter specific gravity.[19] Ljunggren showed that serum hypoglycemia in rats was associated with a brain lactate level of 4.8 Mmoles/g, while hyperglycemia was consistent with a brain lactate level of 20.7 Mmoles/g and a significantly lower intracellular pH.[20]

Increased cerebrospinal fluid lactate levels have been observed in severely brain-injured patients. DeSalles et al.[21] found that ventricular fluid lactate concentration increased within 18 hours after injury in 19 severely head-injured patients (mean GCS on admission, 5.73). Patients with favorable outcome had a significant decrease in ventricular CSF lactate levels by 48 hours after injury. A decrease in lactate was not observed in patients with poor outcomes. Rabow et al.[22] further postulated that CSF lactic acidosis is indicative of a severe, although not necessarily intractable, disturbance of brain function associated with intracellular lactate production and acidosis.

Our data suggest that admission hyperglycemia is a frequent component of the stress response to head injury, a significant indicator of severity of injury, and a significant predictor of outcome from head injury. Studies with cerebral ischemia models show that hyperglycemia adversely affects neurologic recovery. Furthermore Rosner and Becker[23] showed in a cat head injury model that Tris infusion, which countered lactic acidosis, improved survival and morbidity. A randomized prospective study is needed to clarify whether preventing hyperglycemia after head injury improves outcome.

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Discussion

DR. WILLIAM F. COLLINS, JR. (New Haven, Connecticut): I would like to discuss a different aspect before I ask a question. That aspect is how I think some of these findings fit into the studies in general of central nervous system injury. The status of patients with CNS injury when admitted to a hospital has been shown to relate to the outcome. There is the problem of determining what is the best method to treat these patients. The Glasgow coma scale has been an excellent addition to our armamentarium to place patients into mild, moderate, and severe head injury categories and has been helpful in evaluating different types of treatment, particularly when comparing different centers.

Certainly it is no surprise, as Dr. Young has pointed out, that these patients have a stress response. I think the important aspect is that the glucose measurement correlated so well with outcome.

I am sure many of you are aware that during the past 15 years diagnostic imaging has improved the ability to identify mass lesions; intracranial pressure measurements insure that cerebral perfusion is well maintained and arterial oxygen lines eliminate hypo-oxygenation. While these measures have improved CNS injury care, the improvement in the outcome