

# Hyperglycemia after trauma: Physiologic and tolerable or a possible threat that needs to be corrected?

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## Admission hyperglycemia is predictive of outcome in critically ill trauma patients

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### Aim of the study

The purpose of this study was to determine whether admission hyperglycemia was predictive of outcome in critically ill trauma patients.

### Patients and methods

Sung and coworkers collected prospective data on all patients admitted to the R. Adams Cowley Shock Trauma Center and that were admitted also to the intensive care or intermediate care unit over a 2-year period (August 2000–August 2002). Admission serum glucose values were obtained in each patient. Patients were then stratified by admission serum glucose level (<200 mg/dL vs.  $\geq$ 200 mg/dL), age, gender, and Injury Severity Score (ISS). Patients with a preinjury diagnosis of diabetes mellitus were excluded from the analysis of this study to minimize the overlap and confusion between acute stress hyperglycemia and diabetic hyperglycemia. How-

ever, it was possible that they may have included those patients with previously undiagnosed diabetes mellitus as they did not measure hemoglobin A1C levels in their patients.

Medical history was obtained directly from the patient or from the family if the patient was unable to be interviewed. Each patient was screened daily by an infectious disease specialist. The diagnosis of infection was made on the basis of Centers for Disease Control and Prevention criteria. The incidence of infection was defined as follows: the number of patients with infection as the numerator and population at risk as the denominator. Outcome was measured by hospital and intensive care unit length of stay and mortality. Multiple linear regression models were used to evaluate serum glucose as an individual predictor of outcome in relation to other potential risk factors including age, injury severity, and ventilator days.

### Results

A total of 1,003 patients were enrolled in the study. The majority (78%) of the admissions were related to blunt injury and the remainder (22%) were caused by penetrating injuries. Men accounted for the majority of the study population (73%), as compared with 27% women. The mean age of the study population was  $43 \pm 25$  years, with no significant difference between the two study groups. The mean ISS was  $23.5 \pm 9$ , with no sig-

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nificant difference between the two study groups. Two hundred fifty-five patients were admitted with hyperglycemia (serum glucose, >200 mg/dL) over the study period. Although men accounted for the majority of the admissions, women were more likely to be hyperglycemic at admission ( $p=0.015$ ).

Throughout the entire study period a total of 372 patients were diagnosed with infection. Respiratory infections were the most common (35%), followed by genitourinary (22%), bloodstream (18%), intra-abdominal/gastrointestinal (11%), skin/wound (11%), and others (3%). Patients with hyperglycemia had a significantly higher overall infection rate (52% vs. 32%,  $p < 0.001$ ). When evaluated by site-specific infection rate, the hyperglycemic group had a significantly greater respiratory, genitourinary, bloodstream, and skin/wound infection rates.

In terms of outcome, the hyperglycemic group had a significantly greater number of ventilator, hospital days and mortality when evaluated by univariate analysis. When analyzed by multivariate linear regression analysis, hyperglycemic patients had a significantly greater risk of infection, increased number of ventilator days and ultimately, increased intensive care unit and hospital length of stay. In addition, these patients had a 2.2-times greater risk of mortality when adjusted for age and ISS.

## Conclusions

In this study admission hyperglycemia was associated with increased morbidity and mortality in a critically ill general trauma population. It is still unclear whether hyperglycemia was the cause of worsening outcome or just another marker for severity of illness.

## Commentary

The ability of the human body to maintain homeostasis during and acute physical derangement is a basic and important surviving mechanism. A series of autonomic/endocrine adaptive and compensatory changes have developed over millennia by the organism in order to maintain this homeostasis.

Any major insult such as sepsis, surgery or trauma, awakens a series of physiologic and endocrinological changes known as the hypermetabolic stress response [1, 2]. Trauma patients represent a unique patient population as the hypermetabolic response to injury is driven by an increase in the activity of the hypothalamus and sympathetic nervous system that leads to an increased release

of ACTH, catecholamines, and glucagon [3]. Stress carbohydrate metabolism in these patients is characterized by increased glycogenolysis and gluconeogenesis with an increased glucagon/insulin ratio [4]. These acute changes lead to hyperglycemia [3-4].

In critically ill patients, Van den Berghe and associates found that trying to maintain blood glucose at or below 110 mg/dL with the help of intensive insulin therapy, had a significant effect on morbidity and mortality [5]. Prior to this study, hyperglycemia was always considered as an integral part of the hypermetabolic stress response and blood glucose levels up to 215 mg/dL were tolerated before insulin therapy was initiated [6-9].

Why does hyperglycemia affect the outcome in trauma patients? Recent studies have shown that both insulin and glucose can affect the systemic inflammatory response [10-14]. It has been found that high plasma glucose concentrations impair immune function by altering cytokine production from macrophages, diminishing lymphocyte proliferation and depressing intracellular bacterial activity of leukocytes [15, 16]. A reduction in chemotaxis, adherence to vascular endothelium, phagocytosis and cell-mediated immunity has also been described [10]. Furthermore, glucose concentrations above 200 mg/dL have been shown to glycosylate immunoglobulins causing a significant reduction in opsonic activity [16]. As a result, the presence of elevated blood glucose impedes normal host defenses against infection and impairs normal inflammatory response [10].

There are several advantages of aggressive glycemic control in trauma patients. For example, insulin by itself may help improve systemic inflammatory response to trauma even without hyperglycemia [17-20]. In a thermally injured children group, Jeschke and coworkers found that those patients that received insulin had lower levels of pro-inflammatory cytokines; had increased levels of constitutive-hepatic proteins and also required less albumin administration for volume [21]. This might be due to a new found anti-inflammatory activity of insulin that acts by inhibition of the production of nuclear factor Kappa  $\beta$  which is a proinflammatory mediator [22, 23].

The study by Sung is important as it shows that admission hyperglycemia in trauma patients is predictive of outcome and therefore, measures to control it are likely to improve the outcome of these patients.

## Conclusions

Admission hyperglycemia is associated with an increased morbidity and mortality in the critically ill trauma

population studied by Sung and coworkers. There are a variety of mechanisms involved and attempts to control

the glycemic index should become routine in the management of these patients.

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