HYPERGLYCEMIA HAS A STRONGER RELATION WITH OUTCOME IN TRAUMA PATIENTS THAN IN OTHER CRITICALLY ILL PATIENTS

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ABSTRACT

Background
Acute hyperglycemia is associated with adverse outcome in critically ill patients. Glucose control with insulin improves outcome in surgical intensive care unit (SICU) patients, but the effect in trauma patients is unknown. We investigated hyperglycemia and outcome in SICU patients with and without trauma.

Methods
A 12-year retrospective study was performed at a 12-bed SICU. We collected the reason for admission, Injury Severity Scores (ISS), and 30-day mortality rates. Glucose measurements were used to calculate the hyperglycemic index (HGI), a measure indicative of overall hyperglycemia during the entire SICU stay.

Results
In all, 5234 nontrauma and 865 trauma patients were studied. Trauma patients were younger, more frequently male, and had both lower median admission glucose (123 versus 133 mg/dL) and HGI levels (8.9 vs. 18.4 mg/dL) than nontrauma patients (p < 0.001). Mortality was 12% in both groups. Area under the receiver-operator characteristic for HGI and mortality was 0.76 for trauma patients and 0.58 for nontrauma patients (p < 0.001). In multivariate analysis, HGI correlated better with mortality in trauma patients than in nontrauma patients (p < 0.001). Head-injury and nonhead-injury trauma patients showed similar glucose levels and relation between glucose and mortality.

Conclusions
The relation of hyperglycemia and mortality is more pronounced in trauma patients than in SICU patients admitted for other reasons. The different behavior of hyperglycemia in these patients underscores the need for evaluation of intensive insulin therapy in these patients.
INTRODUCTION

Acute hyperglycemia caused by acute disease is associated with adverse outcome. This association has been demonstrated in patients suffering from trauma\(^1\)–\(^3\), myocardial infarction\(^4\), and stroke\(^5\), as for both general ICU patients\(^6\) and patients admitted to the hospital ward\(^7\). Numerous reports have documented the relation of early hyperglycemia with outcome in trauma patients\(^8\)–\(^16\). Numerous studies have concentrated on early hyperglycemia (i.e., hyperglycemia at admission or during the first 24 hours) in head injury patients. Although glucose levels after the first day have been studied in conjunction with hormone levels or with age\(^17\)–\(^20\), their relation with outcome has not been previously extensively studied, as all prior studies included less than 50 patients. Similarly, although some investigators have compared hormonal levels in trauma patients with and without head injury\(^18\),\(^20\), no study compared the association between hyperglycemia and outcome directly in these two patient groups. Two intervention studies have showed improvement in outcome after strict treatment of hyperglycemia in the intensive care unit\(^21\),\(^22\). However, trauma patients only made up 4.4%\(^21\) and 5.4%\(^22\) of the study subjects and therefore the effect of this intervention on trauma patients remains unclear. To elucidate the possible value of intensive insulin therapy in trauma patients, we performed a retrospective study to analyze how changes in glucose relate to mortality in subgroups of ICU patients with various reasons for admission, focusing especially on differences between trauma patients and nontrauma patients. To assess overall glucose control during a longer period than 1 or 2 days, we have developed the hyperglycemic index (HGI). HGI is calculated from all the glucose measurements taken during the entire length of stay at the ICU for a single patient\(^23\). In contrast to admission glucose, HGI reflects hyperglycemia that is amenable to insulin therapy. Within the trauma group, we also analyzed the difference between patients with and patients without head injury.

MATERIALS AND METHODS

Patients and Treatment

Our study retrospectively analyzed all patients over 15 years of age admitted from 1990 through 2001 to the surgical intensive care unit (SICU) of the Groningen University Hospital, a tertiary teaching hospital and Level I trauma center. Patients with no glucose measurements were excluded. Enteral nutrition was started as soon as possible after admission, whereas parenteral nutrition was infrequently used. Insulin treatment was conservative, as insulin administration was only started when glucose levels reached 180 mg/dL; insulin was never administered above 10 IU/h. Except for liver transplant patients, steroids were not routinely used.
Age, sex, reason for admission and all glucose measurements taken during the ICU stay were retrieved from the central hospital information database. The Injury Severity Score (ISS)\textsuperscript{24} as well as International Classification of Diseases (ICD)-9 codes were recorded for trauma patients. ICD diagnoses for closed or penetrating skull or cerebral injuries were used to categorize these patients as suffering from head injury or not. Admission glucose was defined as the first glucose measurement upon arrival at the ICU. See Vogelzang et al.\textsuperscript{23} for the exact calculation of HGI. The hyperglycaemic index corrects for irregular sampling intervals and is not erroneously lowered by hypoglycemic episodes, as HGI only measures levels higher than 108 mg/dL (6.0 mmol/L). HGI can be viewed as the mean glucose level above 108 mg/dL. Therefore, the HGI yields a better estimate of overall glucose control than a single value at admission or the highest value during the first day. Mean glucose levels of all patients were calculated at fixed intervals of 12 hours after admission by linearly interpolating glucose measurements. Hypoglycemia was defined as a measurement lower than 54 mg/dL (3.0 mmol/L). The primary endpoint of this study was 30-day mortality.

Statistical analysis
Data are presented as medians and interquartile range (IQR) for both continuous and ordinal variables. When comparing groups, Student’s t test, the Mann-Whitney U test, or Fisher’s exact test were used when appropriate. Univariate analysis of glucose parameters and mortality was performed by calculating receiver-operator characteristics (ROC) curves. Multivariate analysis was performed by means of binary logistic regression that controlled for age, sex, and ISS (for trauma patients). All evaluated parameters were entered in the model. Odds ratios for glucose-related parameters were calculated for increases of 10 mg/dL. Significance of differences between odds ratios was calculated as described by Altman and Bland\textsuperscript{25}. Statistics were performed with the SPSS statistical package (version 10.0.7, SPSS Inc, Chicago, IL) and Excel (version 97-SR 2, Microsoft Corporation. Redmond, WA).

RESULTS
During the study period, 6,099 out of 6,307 admissions (97%) met the inclusion criteria. Overall mortality was 12%. The reasons for admission were trauma (N = 865, mortality 12.4%), abdominal surgery (N = 2256, mortality 10.8%), liver transplantation (N = 552, mortality 9.1%), vascular surgery (N = 921, mortality 13.5%), and miscellaneous (N = 1505, mortality 14.2%). As trauma patients were the focus of our study, and as univariate correlation between hyperglycemia and outcome was similar for all nontrauma groups (see Fig. 2), we will present only differences between trauma patients and nontrauma patients.
Trauma patients significantly differed from those without trauma in several demographics: age, length of stay, admission glucose, and HGI (all \( p < 0.001 \), Table 1). The median (IQR) ISS for all trauma patients was 21 (13 – 29). Hypoglycemia occurred in 14 trauma patients (1.6%) and in 190 patients without trauma (3.5%, \( p = 0.001 \)). Of the trauma patients, 402 (46%) had head injury. Patients with head injury were younger, had higher ISS scores, and stayed longer at the ICU, and died of different causes than those without head injury (Table 2). Mortality in patients without head injury was 11% compared with 14% in patients with head injury (\( p = 0.01 \)).

Figure 1, A and B shows mean glucose levels from admission to 5 days after admission for patients with and without trauma. As demonstrated by HGI levels in Table 1, patients without trauma had higher overall mean glucose levels than trauma patients.
Table 1. General characteristics of patients studied

<table>
<thead>
<tr>
<th></th>
<th>Nontrauma</th>
<th>Trauma</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5234</td>
<td>865</td>
<td></td>
</tr>
<tr>
<td>Male N (%)</td>
<td>3204 (61)</td>
<td>642 (74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mortality N (%)</td>
<td>631 (12)</td>
<td>107 (12)</td>
<td>0.78</td>
</tr>
<tr>
<td>Age (years)¹</td>
<td>62 (49 – 71)</td>
<td>38 (25 – 77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of stay (days)¹</td>
<td>1.6 (0.9 – 4.6)</td>
<td>2.6 (1.1 – 7.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of glucose measurements / day¹</td>
<td>2.3 (1.7 – 3.6)</td>
<td>1.7 (1.3 – 2.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission glucose (mg/dL)¹</td>
<td>133 (106 – 171)</td>
<td>123 (103 – 151)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperglycemic index (mg/dL)¹</td>
<td>18.4 (4.6 – 44.2)</td>
<td>8.9 (1.8 – 26.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

¹ median (interquartile range)

Nonsurvivors displayed higher glucose values than survivors in the trauma group as well as in the group with other conditions (Figure 1). Moreover, the trauma group showed a greater difference in mean glucose levels between survivors and nonsurvivors than the nontrauma group. A selection effect could play a role in this kind of figure as a large number of patients left the ICU during the first 5 days. However, the same analysis of patients who stayed 5 days or longer displayed a similar pattern.

Figure 2 shows ROC curves of HGI and mortality in all subgroups. The area under the curve for nontrauma patients was low (0.56 for abdominal surgery, 0.61 for liver transplantation, 0.62 for vascular surgery, and 0.57 for miscellaneous). All nontrauma groups together had an area under the curve of 0.58 versus 0.76 for trauma patients (p < 0.001). For head injury patients, the area under the ROC was 0.79 and trauma patients without head injury had an area of 0.72 (p = 0.20). The area under the curve for HGI was

Figure 2. Receiver-operator characteristics for 30-day mortality and Hyperglycemic index in ICU patients with different reasons for admission. Areas under the curve are 0.76 for trauma, 0.56 for abdominal surgery, 0.61 for liver transplant, 0.62 for vascular surgery and 0.57 for miscellaneous.
bigger compared with admission glucose in all subgroups. The area under the ROC for ISS in all trauma patients was 0.66.

Multivariate analysis revealed that HGI correlated significantly better with mortality in patients with trauma than in patients without trauma (Table 3, \( p < 0.001 \)). Of admission glucose and HGI, only HGI is a significant parameter in the multivariate model (\( p < 0.001 \)). Further analysis of the trauma group showed no significant differences in odds ratios of measured variables between head injury and non-head injury patients, apart from age, for which the odds ratio (95% confidence interval) was 1.01 (1.00 – 1.03) in head injury patients and 1.05 (1.03 – 1.07) in patients without head injury (\( p = 0.006 \)).

### Table 2. Characteristics of trauma patients with and without head injury

<table>
<thead>
<tr>
<th></th>
<th>Non-head injury</th>
<th>Head injury</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>463</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>Male sex N (%)</td>
<td>327 (71)</td>
<td>315 (78)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mortality N (%)</td>
<td>49 (11)</td>
<td>58 (14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (years)(^1)</td>
<td>42 (27 – 68)</td>
<td>32 (23 – 50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of stay (days)(^1)</td>
<td>2.1 (1.0 – 6.3)</td>
<td>3.0 (1.5 – 10.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission glucose (mg/dL)(^1)</td>
<td>119 (101 – 150)</td>
<td>124 (104 – 155)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperglycemic index (mg/dL)(^1)</td>
<td>8.2 (1.12 – 2.7)</td>
<td>9.8 (2.4 – 29.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Injury Severity Score(^1)</td>
<td>16 (9 – 25)</td>
<td>25 (18 – 34)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\(^1\) median (interquartile range)

### Table 3. Results of binary logistic regression analysis of factors influencing 30-day mortality

<table>
<thead>
<tr>
<th></th>
<th>Nontrauma patients</th>
<th>Trauma patients</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02 – 1.04)*</td>
<td>1.03 (1.02 – 1.04)*</td>
<td>0.74</td>
</tr>
<tr>
<td>Male</td>
<td>1.16 (0.97 – 1.38)</td>
<td>0.96 (0.57 – 1.61)</td>
<td>0.49</td>
</tr>
<tr>
<td>Admission glucose (per increase of 10 mg/dL)</td>
<td>0.99 (0.97 – 1.00)</td>
<td>0.98 (0.89 – 1.08)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hyperglycemic index (per increase of 10 mg/dL)</td>
<td>1.10 (1.07 – 1.13)*</td>
<td>1.46 (1.29 – 1.65)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>-</td>
<td>1.09 (1.07 – 1.12)*</td>
<td></td>
</tr>
</tbody>
</table>

Data are odds ratios (95% CI) * Significant, \( p < 0.001 \)
DISCUSSION

The relation between hyperglycemia and outcome depended upon reason of admission and was stronger in trauma patients than in other types of critically ill patients, regardless of the presence of head injury. Nonsurviving trauma patients showed marked early hyperglycemia, whereas surviving trauma patients sustained only minor hyperglycemia. Remarkably, glucose levels and their relation with outcome were similar in trauma patients with and without head injury. The hyperglycemic index was superior to admission glucose in discriminating survivors and nonsurvivors in all subgroups.

It must be noted that this study was conducted at an SICU and not at an emergency department. Therefore, patients might already have undergone surgery or other therapy before the admission glucose level was recorded. This may explain why admission glucose and ISS were not as strongly correlated with outcome as in studies that utilize glucose levels from the emergency department\cite{2,9,12–16}. However, this does not affect the relevance of this study, as intensive insulin therapy is mostly advocated while patients are treated at an ICU. Another limitation is that we did not include confounding factors such as caloric intake, steroid use, history of diabetes, and insulin use.

Injury-induced hyperglycemia was already recognized by Claude Bernard. Injury causes an immediate surge of catecholamines in the blood\cite{26}. The stress response to trauma or surgery causes a hypermetabolic state, characterized by protein and fat catabolism, negative nitrogen balance, hyperglycemia, and insulin resistance\cite{27,28}. Although peripheral uptake of glucose as well as cellular glucose utilization is enhanced, increased gluconeogenesis and insulin resistance may prevail, leading to hyperglycemia\cite{29}. The stress response provides a plausible link between injury and the rise in glucose. Glucose levels have been shown to correlate with catecholamine levels in general trauma patients and patients with head injury\cite{12,18,20,26}.

Previously a causal relation has been suggested between glucose and outcome in head injury patients. Assuming hyperglycemia increases anaerobic metabolism and subsequently higher intracerebral lactate levels, low pH levels causing secondary brain damage may result\cite{9–14}. However, De Salles and colleagues have found that cerebrospinal fluid lactate levels stayed high for more than 5 days after trauma, when blood glucose had already normalized\cite{30}, obscuring a direct relation. Recently, Diaz-Parejo and colleagues have measured intracerebral lactate levels during both normoglycemia and hyperglycemia. They found that intracerebral lactate concentration only increased when blood glucose values were over 270 mg/dL, and thus is less likely to play a role at more modest levels of hyperglycemia\cite{31}. Our finding of similarity in the relation between hyperglycemia and mortality in head injury and non-head injury patients could also indicate that other mechanisms, common to both patient groups, are present.
We think the notably different glucose profiles of trauma patients and other ICU patients can be explained by their different baseline characteristics. Trauma patients are significantly younger than other ICU patients and suffer only from trauma, whereas general ICU patients are often older, and more often than not suffer from multiple conditions. Injury drives the stress response, and young trauma patients are able to build up a powerful reaction. Therefore, hyperglycemia might reflect severity of illness better in trauma patients than in general ICU patients. Previous investigators have found that adding additional severity of illness scores into their multivariate model diminishes the role of glucose in predicting outcome. Whether the strong correlation between hyperglycemia and outcome is caused by confounding factors like severity of illness or by a causal relation cannot be concluded from this or any other retrospective study. We think that the differences found in this retrospective study justify the conclusion that regarding hyperglycemia, trauma patients differ from other ICU patients. Furthermore, even with our very conservative insulin protocol, surviving trauma patients only had very modest hyperglycemia as shown in Figure 1 and reflected in their HGI of only 9 mg/dL, which is equivalent to a mean glucose level of 117 mg/dL.

Thorell and colleagues recently investigated how intensive insulin therapy leads to normoglycemia in critically ill trauma patients. They showed that insulin reduces endogenous glucose production, whereas whole-body glucose disposal is not increased. The mechanism behind the impressive results of intensive insulin therapy in the study by van den Berghe and colleagues is still largely unknown. Multiple theories have been proposed, including a decreased infection rate due to improved macrophage function, reduced endothelial dysfunction, improvement of lipid disorders, and reduced hyperglycaemic axonal damage. These general mechanisms may apply to every critically ill patient and, therefore, proponents advocate intensive insulin therapy in all critically ill patients, regardless of underlying illness. However, retrospective data incompatible with this theory is available; Laird and colleagues did not find a significant relation between infection and hyperglycemic levels on day 1 or 2 in trauma patients. Yendamuri and colleagues did find a significant relation between admission glucose and urinary tract infection and a borderline significant trend toward increased incidence of pneumonia, but no increased rate of bacteremia or wound infection. More important, few trauma patients were included in the two intervention studies that actually implemented strict glucose control by intensive insulin therapy. In the Leuven study (a randomized controlled trial), the mortality in the trauma group was 8.6% in the conventional group (N = 35) and 12.1% in the intervention group (N = 33). In the study by Krinsley (a “before - after” study), the mortality rates were 17.8% and 19.5%, respectively (N = 48 and 38). The trend toward higher mortality is remarkable regarding the Acute Physiology and Chronic Health Evaluation (APACHE-II) scores, which were significantly lower in the intervention group.
CONCLUSIONS

Our results show that trauma patients differ from patients with other reasons for admission. It is likely that different mechanisms play a role in glucose homeostasis in patient groups with different baseline characteristics. Caution is to be exercised when implementing insulin therapy in trauma patients. A randomized controlled trial in a large group of trauma patients is needed to bring the value of glucose control in trauma patients to light.

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REFERENCES