Hyperglycemia is an independent predictor of in-hospital mortality in critically ill patients with acute kidney injury-a cohort study

Maristela Bohlke,* Laura Madeira, Tulio Reichert, Ana Carolina Brochado Geist, Pedro Funari Pereira, Helena Rotta Pereira, Gustavo Tragnago, Paulo Caruso, Franklin Correa Barcellos

Dialysis and Transplantation Unit, São Francisco de Paula University Hospital, Catholic University of Pelotas, Brazil

Received: October 20, 2015          Accepted: November 8, 2015          Online Published: November 21, 2015
DOI: 10.5430/jer.v2n1p102          URL: http://dx.doi.org/10.5430/jer.v2n1p102

ABSTRACT

Introduction: The association of hyperglycemia with poor outcomes has been described in several settings, including in general intensive care unit (ICU) patients. However, it is not clear whether this relationship is consistent for all critically ill patients. Our study assessed the association of blood glucose (BG) with in-hospital mortality in critically ill patients with acute kidney injury (AKI).

Methods: A cohort of critical care patients with AKI was followed up until death or hospital discharge. The association of BG level with in-hospital mortality was analyzed with multivariate logistic regression analysis adjusted for demographic, socioeconomic, laboratory and clinical variables. Receiver-operating characteristics (ROC) analysis was used to assess the ability of various levels of BG to predict in-hospital mortality.

Results: One hundred patients were followed, with a mean age of 62.2 years, 49 male, 41 surgical, 34 diabetics and 63 with sepsis. Nineteen patients needed renal replacement therapy and 67 died during hospital stay. In the final multivariate model, age, glucose level and sepsis had an independent association with the outcome death. The threshold level of BG that maximized the combined sensitivity and specificity for the prediction of in-hospital mortality by ROC analysis was 109 mg/dl. In the stratified analysis, BG was an independent predictor of death only among non-diabetic patients.

Conclusions: To the best of our knowledge, this is the first study to describe an association between hyperglycemia and in-hospital mortality in critically ill patients with AKI. Further studies are needed to confirm this finding and to assess the potential impact of tighter glucose control in this subpopulation.

Key Words: Acute kidney injury, Hyperglycemia, Intensive care unit, Mortality

1. INTRODUCTION

Despite significant improvements in intensive care medicine, the prognosis of acute kidney injury (AKI) patients remains poor, with mortality rates ranging from 40% to 65%.[1] Several factors may contribute to the high mortality rate of AKI, including the underlying disease,[2-5] the circumstances leading to the development of AKI[3-7] and the severity of illness.[3,8] In addition, the need for therapeutic measures such as mechanical ventilation and the use of vasoactive drugs have been demonstrated to be related to intensive care unit

*Correspondence: Maristela Bohlke, Project Coordinator; Email: mbohlke.sul@gmail.com; Address: Dialysis and Transplantation Unit, São Francisco de Paula University Hospital, Catholic University of Pelotas, Brazil.
(ICU) mortality in patients with AKI."^{[4,9]} None of these mortality predictors can be subject of a broadly applicable preventive approach.

Although extensive research efforts during the last decade focused on strategies to improve prognosis in the potentially lethal multiple organ failure, only few of them revealed positive results."^{[10–13]} One of these strategies is blood glucose control with insulin."^{[13]}

Evidence that hyperglycemia is associated with increased morbidity and mortality has been reported for a variety of disorders and settings, including acute myocardial infarction,"^{[14–24]} stroke,"^{[25,26]} the general ICU,"^{[27,28]} coronary artery bypass graft surgery,"^{[29,30]} trauma,"^{[31–35]} cerebral endarterectomy,"^{[36]} congestive heart failure,"^{[37,38]} chronic obstructive pulmonary disease,"^{[39]} and hospitalized pediatric patients."^{[1,40]} Collectively, these reports strongly suggest that inpatient hyperglycemia is associated with adverse outcomes. Because some intervention studies of glucose lowering with insulin have demonstrated improved outcomes,"^{[13]} it appears that elevated glucose is a causal rather than just a severity of disease marker factor.

Despite the available evidence, it is not clear whether the relation between acute hyperglycemia and increased mortality risk is consistent for all critically ill hospitalized patients. To address this concern, our study was conducted assessing whether mortality of critically ill AKI patients is associated with blood glucose (BG) level.

2. METHODS

2.1 Study design

It was a cohort study conducted in a general ICU from a southern Brazilian University Hospital. All patients admitted to the ICU during a period of 18 months who developed acute kidney injury were included in the study. The ICU was visited daily by the investigators screening for new cases of AKI. All eligible patients were evaluated on the first day of AKI diagnosis. After inclusion, the patients were followed up daily by investigators with record of need for renal replacement therapy (RRT) and/or death. The patients were followed up until death or hospital discharge.

2.2 Data collection and management

The covariates include age, gender, time since admission to ICU, comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, human immunodeficiency virus infection, heart failure, cancer and chronic liver disease), cause of ICU admission, precipitating factors for AKI, presence of sepsis, use of vasoactive drugs, mechanical ventilation, oxygen inspiratory fraction, urine output (UO), mean arterial pressure, central venous pressure, laboratory variables (oxygen arterial pressure, bicarbonate, arterial pH, creatinine, blood glucose, albumin, hematocrit). APACHE II score and RIFLE classification for AKI was applied in the same day of AKI diagnosis. It was registered the lower mean arterial pressure and the higher central venous pressure in the AKI diagnosis day. These data were recorded only at baseline, i.e., within the first 24 hours after diagnosis of AKI.

2.3 Definitions

Prerenal AKI was considered present when treatment with volume repletion and/or improvement in cardiac output was rapidly successful in restoring renal function. Sepsis was defined as the systemic response to infection, manifested by 2 or more of the following conditions as a result of infection: (1) temperature greater than 38°C or less than 36°C, (2) heart rate greater than 90 beats/min, and (3) respiratory rate greater than 20 breaths/min or arterial CO\(_2\) pressure less than 32 mmHg and (4) white blood cell count greater than 12,000/ml, less than 4,000/ml, or greater than 10% immature (band) forms."^{[42]}

The definition of AKI used to access eligibility of patients for the study was based on RIFLE criteria, with inclusion of patients classified in Injury or Failure severity classes. The acronym RIFLE stands for the increasing severity classes of AKI, risk (R), injury (I), and failure (F), and the two outcome classes, loss (L) and end-stage kidney disease (E)."^{[43]}

The three severity grades are defined on the basis of the changes in serum creatinine or UO, in which the worst of each criterion is used. Class R is defined by an increase of creatinine × 1.5 or GFR decrease > 25% or UO < 0.5 ml/kg/h × 6 hr; class I occurs if occurs an increase of creatinine × 2 or GFR decrease > 50% or UO < 0.5 ml/kg/h × 12 hr; class F is characterized by increase of creatinine × 3 or GFR decrease >75% or creatinine ≥ 4 mg/dl with an acute rise of ≥ 0.5 mg/dl or UO < 0.3 ml/kg/h × 24 hr or anuria × 12 hrs. The two outcome criteria, loss and end-stage kidney disease, are defined by the duration of loss of kidney function; these two criteria were not evaluated in this study. Blood glucose was obtained after an overnight fasting of 8 hours within 24 hours of the AKI diagnosis. Plasma glucose was enzymatically determined with the glucose oxidase method using an A25 Random Access Analyzer (Biosystems).

Patients were classified as having diabetes on the basis of history, regardless of duration of disease, or need for antidiabetic agents. The diagnosis was established if the patient had been informed of the diagnosis by a physician before the admission and had been prescribed oral antihyperglycemic agents, insulin, or diet therapy.
Ethical aspects: The local Ethics Committee approved the research project. All participants or relatives accepted the inclusion in the study by signing an informed consent.

2.4 Statistical analysis

Data were analyzed using the Stata 11.2 software (Stata Corporation, College Station, TX, USA). The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify the normality of distribution of continuous variables. Non-parametric measures of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the two-tailed t test, Mann-Whitney U test, chi-square test, and Fisher exact test as appropriate.

The skewed distributed variables were submitted to transformation searching for normality. Stepwise multivariate logistic regression analysis was used to investigate independent associations between mortality and variables that had showed some association \((p < .25)\) with outcome in previous univariate analysis. Once the multivariate model was built, the variables that did not keep a statistically significant association with the outcome were successively excluded from the model, beginning with those which had the lowest association. The likelihood ratio (LR) test between the models with and without the variable being excluded and the b-coefficients of the remaining variables were evaluated. In the case which the likelihood ratio test showed significant change or if there were important changes in the coefficient of the other variables, the variable in process of exclusion was reinserted in the model, independently of the significance was set at \(P\) calculated. Statistical tests were 2 sided, and the level of significance was the 75th percentile of BG.

The relationship of BG and calculation of death percentage inside each stratus. The cutoff point of 110 was chosen based on results of previous studies that showed that decreasing glucose below this level decreased mortality. Another cutoff was the 75th percentile of BG.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical tests were 2 sided, and the level of significance was set at \(P\) less than .05.

3. RESULTS

There were 421 admissions in the studied ICU during the 18 months of follow-up. Among these patients there were 100 cases of acute kidney injury. These patients had a mean age of 62.2 years, 49 were male, 41 were surgical patients, 34 had diabetes, 63 had a sepsis diagnosis and their median time in ICU before AKI diagnosis was two days. Nineteen patients needed RRT and 67 died during hospital stay. Table 1 describes sample characteristics according to outcome.

Table 1. Sample characteristics according to outcome \((n = 100)\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survival ((n = 33))</th>
<th>Death ((n = 67))</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ((\text{mean/sd}))</td>
<td>60.2(17)</td>
<td>63.3(16.7)</td>
<td>.19</td>
</tr>
<tr>
<td>Male %(\text{male})</td>
<td>57.6</td>
<td>44.8</td>
<td>.2</td>
</tr>
<tr>
<td>APACHE II score ((\text{mean/sd}))</td>
<td>22.6(7.3)</td>
<td>29.2(7.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RIFLE F %(\text{F})</td>
<td>60.6</td>
<td>63.6</td>
<td>.9</td>
</tr>
<tr>
<td>Surgical patients %(\text{p})</td>
<td>36.4</td>
<td>43.3</td>
<td>.5</td>
</tr>
<tr>
<td>Sepsis diagnosis %(\text{Diagnosis})</td>
<td>50</td>
<td>72.7</td>
<td>.03</td>
</tr>
<tr>
<td>Time since ICU (\text{admission\ (days)})\ (median/range)</td>
<td>1(0-16)</td>
<td>2(0-25)</td>
<td>.4</td>
</tr>
<tr>
<td>Vasoactive drugs %(\text{V})</td>
<td>36.4</td>
<td>62.7</td>
<td>.01</td>
</tr>
<tr>
<td>Mechanical ventilation %(\text{Mechanical})</td>
<td>39.4</td>
<td>80.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FiO2 (\text{mean/sd}))</td>
<td>21(21-100)</td>
<td>47.5(21-100)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glasgow (\text{median/range}))</td>
<td>14(3-15)</td>
<td>6(3-15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma creatinine (\text{mg/dl\ (median/range)})</td>
<td>2.65(2-14.6)</td>
<td>2.73(2-10.5)</td>
<td>.45</td>
</tr>
<tr>
<td>Oliguria %(\text{O})</td>
<td>15.1</td>
<td>35.8</td>
<td>.03</td>
</tr>
<tr>
<td>RRT %(\text{R})</td>
<td>15.1</td>
<td>21.2</td>
<td>.4</td>
</tr>
<tr>
<td>Lowest MAP (\text{median/range}))</td>
<td>73.3(50-106.6)</td>
<td>66.6(0-106.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Highest CVP (\text{median/range}))</td>
<td>14(1-28)</td>
<td>13(5-40)</td>
<td>.2</td>
</tr>
<tr>
<td>Potassium (\text{mEq/L\ (mean/sd)})</td>
<td>4.2(1)</td>
<td>4.4(0.9)</td>
<td>.26</td>
</tr>
<tr>
<td>Arterial bicarbonate (\text{mEq/L\ (mean/sd)})</td>
<td>18.8(6.5)</td>
<td>16.7(7.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Hematocrit %(\text{mean/sd})</td>
<td>32.9(7)</td>
<td>32.9(7.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Blood glucose (\text{mg/dl\ (median/range)})</td>
<td>95(76-163)</td>
<td>123(35-413)</td>
<td>.15</td>
</tr>
<tr>
<td>Albumin (\text{g/dl\ (median/range)})</td>
<td>2.15(1.4-5.9)</td>
<td>2.1(1.1-3.5)</td>
<td>.9</td>
</tr>
</tbody>
</table>

Note. FiO2 = oxygen inspiratory pressure; RRT = renal replacement therapy; MAP = mean arterial pressure; CVP = central venous pressure.

Twenty participants (20%) did not have BG measured in the day of AKI diagnosis. The outcomes were compared between these patients and those who had a BG measurement, to determine whether missing values may have confounded the results. The mortality rate was similar in both groups (32% vs. 42%, \(p = .3\)), likewise APACHE II score (25.8 vs. 27.7, \(p = .16\)).

ISSN 2377-9306  E-ISSN 2377-9330
The patients who died presented a lower mean blood pressure and a greater percentage of need for vasoactive drugs and mechanical ventilation, more sepsis and oliguria cases, lower Glasgow scale, greater APACHE II score, and they needed a greater oxygen inspiratory pressure (see Table 1).

Besides the above described variables, which presented significant association with death in univariate analysis, it had been included in the multivariate model the variables age, gender, central venous pressure and plasma glucose because these variables had a tendency of association with death ($p < .25$).

In the final multivariate model, age, blood glucose, and sepsis diagnosis had a significant and independent association with the outcome death. The central venous pressure was maintained in the model despite its not significant association with mortality because its exclusion led to a significant change in the likelihood ratio test (see Table 2).

**Table 2.** Logistic regression model for predictors of death including all patients, log likelihood = -10.04, pseudo $R^2 = 0.48$

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.11</td>
<td>0.05</td>
<td>1.01-1.21</td>
</tr>
<tr>
<td>Sepsis</td>
<td>107.49</td>
<td>237.19</td>
<td>1.42-8121.97</td>
</tr>
<tr>
<td>BG</td>
<td>1.09</td>
<td>0.05</td>
<td>1.00-1.20</td>
</tr>
<tr>
<td>Highest CVP</td>
<td>1.07</td>
<td>0.08</td>
<td>0.91-1.26</td>
</tr>
</tbody>
</table>

Note. OR = odds ratio; SE = standard error; BG = blood glucose; CVP = central venous pressure.

Because the selection of a “normal” value for BG in the setting of acute kidney injury in ICU patients is likely to be somewhat arbitrary, receiver-operating characteristics curves of the ability of various glucose levels to predict in-hospital mortality were plotted. The threshold levels of BG of 109 mg/dl maximized the combined sensitivity and specificity for the prediction of in-hospital mortality. (see Figure 2)

In the subgroup analysis of diabetic patients ($n = 34$), postoperative status (OR 38.8 CI 95% 1.1-1.410.3 $p = .04$) and hematocrit (OR 1.33 CI 95% 1.0-1.8 $p = .04$) were associated with greater mortality rates. Oliguria (OR 64.7 CI 95% 0.7-5.854.2 $p = .07$) showed a tendency of association, and there was no association of blood glucose with mortality rate among diabetic patients.

Among non-diabetic patients, the prediction model for mortality included central venous pressure, age, sepsis and BG. Age, central venous pressure and sepsis were kept in the model because their exclusion led to significant changes in LR test. The blood glucose level was the only variable inde-
pendently and significantly associated with mortality among non-diabetic patients. (see Table 3)

4. DISCUSSION

The association between hyperglycemia and poorer outcomes has been described in several clinical and surgical settings, including in intensive care unit patients. It is also well-known the increased risk for the development of acute kidney injury associated with hyperglycemia in a series of disease states.\[13, 44, 45\] Nevertheless, the association between higher glucose level and mortality in acute kidney injury patients had not yet been described.

Hyperglycemia is a frequent complication of acute diseases or injuries. These situations bring about hormonal changes, cytokines release, and nervous system activation which affect glucose metabolic pathways, increasing insulin resistance, and leading to a condition named “diabetes of injury”.\[46, 47\] Injury-induced hyperglycemia was previously regarded as an beneficial adaptive stress response, facilitating glucose uptake by non-insulin-dependent tissues. Therefore, blood glucose up to 200 mg/dl were recommended during serious acute events.\[48\]

However, the critical care community nowadays is reconsidering this dogma. In 2001, it was published a large, randomized, controlled, clinical study that showed that titrating insulin infusion during intensive care to strict normoglycemia (below 110 mg/dl) strikingly reduced mortality when compared with the conventional insulin treatment.\[13\]

A well conducted meta-analysis of smaller randomized trials examining insulin treatment in critically ill patients found reduced mortality with intervention.\[49\] although other meta-analysis have presented different results.\[50\] Recently, NICE SUGAR,\[51\] a pragmatic study of tight glycemic control conducted in 41 hospitals with recruitment of 6,100 participants, found increased mortality with tight glucose control. However, even patients in the higher range (control) group in this study had their blood glucose controlled to a target of 144-180 mg/dl. The mean time-weighted blood glucose level in the conventional-control group was 144 ± 23 mg per deciliter and more than two thirds of these patients still received intravenous insulin to accomplish this goal. Therefore, even this negative study does not provide enough evidence in favor of abandoning glucose control.

However, there are some key questions that remain unresolved: which subgroups of patients, if any, might still benefit from the more stringent levels of glycemic control? Determine glucose target associated with better outcomes in each disease and setting is fundamental to answer this question.\[52\]

Among AKI patients, there is no conclusive data about the issue. May glucose level in AKI patients have a lower threshold? Our data show a progressive increase in mortality rate from the glucose levels of 110 to 165 mg/dl and above. The ROC analysis found a glucose level of 10^6 mg/dl as the better threshold to predict in-hospital mortality in AKI patients, which suggest that even modest increases of glucose levels may have prognostic implications. In the present study, blood glucose had a significant association with mortality even after adjustment for severity of illness. Thus, hyperglycemia seems to have a moderate impact on mortality, regardless of its role as a severity of disease marker, at least among non-diabetic AKI patients. The greater prognostic implication of hyperglycemia among nondiabetic patients has been described in others disease states.\[14, 25\] Van den Berghe et al., who found a 42% reduction in the relative risk of ICU mortality in the group randomized to tight glucose control, studied only 13% of diabetic patients.\[13\] The diabetics of injury could be more acutely toxic than chronic hyperglycemia due to greater cellular glucose overload, and more pronounced side effects of glycolysis and oxidative phosphorylation. There is also the possibility that the smaller number of diabetic patients results in less power to detect the same association. Furthermore, the definition of stress hyperglycemia is intrinsically problematic in diabetic patients because the unstressed baseline level of glucose is frequently unknown. Finally, diabetic patients are more likely to receive intensive insulin therapy during their ICU stay.

The present data show that blood glucose level was an independent predictor of mortality in this sample of critically ill non-diabetic patients with AKI. Despite the promising results, several limitations should be recognized in this study. First, the study enrolled a small number of patients from a single institution, so there is low external validity. There were only 34 diabetic patients included in the analysis, which precludes any strong conclusion about this subset of patients. Second glucose measurement was performed only on the first day of AKI diagnosis, and a significant proportion of the sample had no glucose measurement. We were also unable to distinguish between stress hyperglycemia and previously undiagnosed glucose intolerance or diabetes mellitus. The hemoglobin-A1C could help to differentiate these groups, but this data was not available in non-diabetics patients. Additionally, there is a lack of data indicating use of dextrose infusions/parenteral nutrition, corticosteroids, and insulin therapy during the ICU stay.

5. CONCLUSIONS

To the best of our knowledge, this is the first study to assess the relation between hyperglycemia and in-hospital mortality in critically ill patients with AKI. In this small and single
center sample, we found an association between higher blood glucose and in-hospital mortality rates among non-diabetic patients. These findings are significant as hypothesis generator, and additional randomized clinical trials are needed to reassess this association and evaluate whether interventions aimed to tighter glucose control in critically ill non-diabetic patients with acute kidney injury could improve their prognosis.

REFERENCES


