ORIGINAL ARTICLES

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

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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

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(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 $\times$ 1.5 or GFR decrease > 25% or UO < 0.5 ml/kg/h $\times$ 6 hr; class I occurs if occurs an increase of creatinine $\times$ 2 or GFR decrease > 50% or UO < 0.5 ml/kg/h $\times$ 12 hr; class F is characterized by increase of creatinine $\times$ 3 or GFR decrease >75% or creatinine $\geq$ 4 mg/dl with an acute rise of $\geq$ 0.5 mg/dl or UO < 0.3 ml/kg/h $\times$ 24 hr or anuria $\times$ 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 analysiss

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 of its association with the dependent variable, considering its role as a possible confounding factor.

Different models were constructed for the overall group, the diabetic group and the nondiabetic group. Receiver-operating characteristics (ROC) analysis was used to assess the ability of various levels of BG to predict in-hospital mortality. The ROC curve indicates the probability of a true-positive result as a function of the probability of a false-positive result for all possible threshold values. The BG was introduced in the multivariate model as continuous variables. The relationship between BG and mortality was further explored by stratification of BG and calculation of death percentage inside each of the 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 chosen 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)

	Survival (n = 33)	Death (n = 67)	*p-value*
Age (mean/*sd*)	60.2(17)	63.3(16.7)	.19
Male (%)	57.6	44.8	.2
APACHE II score (mean/*sd*)	22.6(7.3)	29.2(7.9)	< .001
RIFLE F (%)	60.6	63.6	.9
Surgical patients (%)	36.4	43.3	.5
Sepsis diagnosis (%)	50	72.7	.03
Time since ICU admission (days) (median/range)	1(0-16)	2(0-25)	.4
Vasoactive drugs (%)	36.4	62.7	.01
Mechanical ventilation (%)	39.4	80.3	< .001
FiO_2 (mean/*sd*)	21(21-100)	47.5(21-100)	< .001
Glasgow (median/range)	14(3-15)	6(3-15)	< .001
Plasma creatinine (mg/dl) (median/range)	2.65(2-14.6)	2.73(2-10.5)	.45
Oliguria (%)	15.1	35.8	.03
RRT (%)	15.1	21.2	.4
Lowest MAP (median/range)	73.3(50-106.6)	66.6(0-106.6)	.02
Highest CVP (median/range)	14(1-28)	13(5-40)	.2
Potassium (mEq/L) (mean/*sd*)	4.2(1)	4.4(0.9)	.26
Arterial bicarbonate (mEq/L) (mean/sd)	18.8(6.5)	16.7(7.4)	.14
Hematocrit (%) (mean/*sd*)	32.9(7)	32.9(7.1)	.8
Blood glucose (mg/dl) (median/range)	95(76-163)	123(35-413)	.15
Albumin (g/dl) (median/range)	2.15(1.4-5.9)	2.1(1.1-3.5)	.9

Note. FiO_2 = 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, $p = .16$).

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

	OR	SE	95% IC
Age	1.11	0.05	1.01-1.21
Sepsis	107.49	237.19	1.42-8121.97
BG	1.09	0.05	1.00-1.20
Highest CVP	1.07	0.08	0.91-1.26

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

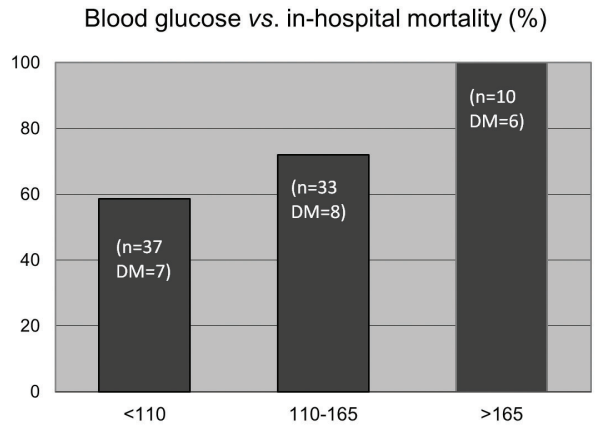

Figure 1. Blood glucose versus in-hospital mortality

The APACHE II score was not associated with mortality in multivariate analysis, but it was forced in the model to control for illness severity. However, as the LR had no difference between the models with and without APACHE score, this variable was excluded from the model.

Within the group of patients with blood glucose concentration at or below 110 mg/dl, the mortality was 58.6%, while 72% and 100% of the patients with glucose between 110-165 mg/dl (75th percentile) and above 165 mg/dl died, respectively. (see Figure 1)

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)

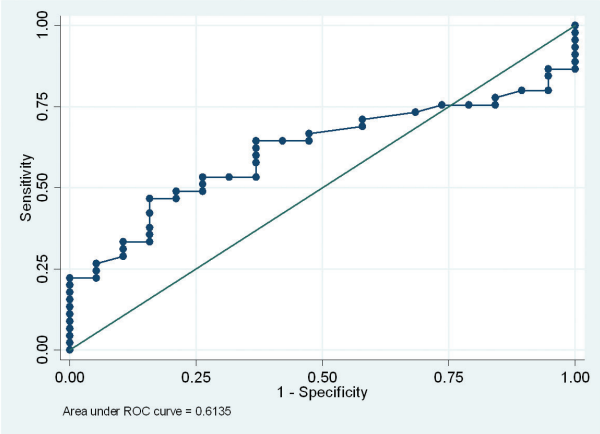

Figure 2. ROC curve for blood glucose level as a predictor of mortality

Table 3. Logistic Regression Model for predictors of death among nondiabetics, log likelihood = -7.75, pseudo R_2 = 0.44

	OR	SE	95% CI
Age	1.09	0.05	0.99-1.20
Sepsis	62.79	153.67	0.51-7604.18
BG	1.10	0.05	1.00-1.22
Highest CVP	1.04	0.08	0.89-1.22

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

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 10^9 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 diabetes 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

[1] Ympa YP, Sakr Y, Reinhart K, *et al*. Has mortality from acute renal failure decreased? A systematic review of the literature. Am J Med. 2005; 118: 827-832. PMid:16084171 http://dx.doi.org/10.1016/j.amjmed.2005.01.069

[2] Jones CH, Richardson D, Goutcher E, *et al*. Continuous venovenous high-flux dialysis in multiorgan failure: a 5-year single-center experience. Am J Kidney Dis. 1998; 31: 227-233. PMid:9469492 http://dx.doi.org/10.1053/ajkd.1998.v31.pm9469492

[3] de Mendonca A, Vincent JL, Suter PM, *et al*. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000; 26: 915-921. PMid:10990106 http://dx.doi.org/10.1007/s001340051281

[4] Uchino S, Kellum JA, Bellomo R, *et al*. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005; 294: 813-818. PMid:16106006 http://dx.doi.org/10.1001/jama.294.7.813

[5] Schroeder TH, Hansen M, Dinkelaker K, *et al*. Influence of underlying disease on the outcome of critically ill patients with acute renal failure. Eur J Anaesthesiol. 2004; 21: 848-853. PMid:15717698 http://dx.doi.org/10.1097/00003643-200411000-00002

[6] Dharan KS, John GT, Antonisamy B, *et al*. Prediction of mortality in acute renal failure in the tropics. Ren Fail. 2005; 27: 289-296. PMid:15957545 http://dx.doi.org/10.1081/JDI-200056612

[7] Loza R, Estremadoyro L, Loza C, *et al*. Factors associated with mortality in acute renal failure (ARF) in children. Pediatr Nephrol. 2006; 21: 106-109. PMid:16252111 http://dx.doi.org/10.1007/s00467-005-2038-y

[8] Wang IK, Wang ST, Chang HY, *et al*. Prognostic value of acute physiology and chronic health evaluation II and organ system failure in patients with acute renal failure requiring dialysis. Ren Fail. 2005; 27: 663-669. PMid:16350815 http://dx.doi.org/10.1080/08860220500234881

[9] Metnitz PG, Krenn CG, Steltzer H, *et al*. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002; 30: 2051-2058. PMid:12352040 http://dx.doi.org/10.1097/00003246-200209000-00016

[10] Amato MB, Barbas CS, Medeiros DM, *et al*. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998; 338: 347-354. PMid:9449727 http://dx.doi.org/10.1056/NEJM199802053380602

[11] Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345: 1368-1377. PMid:11794169 http://dx.doi.org/10.1056/NEJMoa010307

[12] Bernard GR, Vincent JL, Laterre PF, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001; 344: 699-709. PMid:11236773 http://dx.doi.org/10.1056/NEJM200103083441001

[13] van den Berghe G, Wouters P, Weekers F, *et al*. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001; 345: 1359-1367. PMid:11794168 http://dx.doi.org/10.1056/NEJMoa011300

[14] Capes SE, Hunt D, Malmberg K, *et al*. Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000; 355: 773-778. http://dx.doi.org/10.1016/S0140-6736(99)08415-9

[15] Bauters C, Ennezat PV, Tricot O, *et al*. Stress hyperglycemia is an independent predictor of left ventricular remodeling after first anterior myocardial infarction in nondiabetic patients. Eur Heart J. 2007; 28: 546-552. PMid:17314113 http://dx.doi.org/10.1093/eurheartj/ehl546

[16] Ainla T, Baburin A, Teesalu R, *et al*. The association between hyperglycaemia on admission and 180-day mortality in acute myocardial infarction patients with and without diabetes. Diabet Med. 2005; 22: 1321-1325. PMid:16176190 http://dx.doi.org/10.1111/j.1464-5491.2005.01625.x

[17] Goyal A, Mahaffey KW, Garg J, *et al*. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. Eur Heart J. 2006; 27: 1289-1297. PMid:16611669 http://dx.doi.org/10.1093/eurheartj/ehi884

[18] Hadjadj S, Coisne D, Mauco G, *et al*. Prognostic value of admission plasma glucose and HbA in acute myocardial infarction. Diabet Med. 2004; 21: 305-310. PMid:15049930 http://dx.doi.org/10.1111/j.1464-5491.2004.01112.x

[19] Ishihara M, Kojima S, Sakamoto T, *et al*. Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era. Am Heart J. 2005; 150: 814-820. PMid:16209987 http://dx.doi.org/10.1016/j.ahj.2004.12.020

[20] Suleiman M, Hammerman H, Boulos M, *et al*. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. Circulation. 2005; 111: 754-760. PMid:15699267 http://dx.doi.org/10.1161/01.CIR.0000155235.48601.2A

[21] Timmer JR, Ottervanger JP, Bilo HJ, *et al*. Prognostic value of admission glucose and glycosylated haemoglobin levels in acute coronary syndromes. QJM. 2006; 99: 237-243. PMid:16504985 http://dx.doi.org/10.1093/qjmed/hcl028

[22] Timmer JR, van der Horst, IC, Ottervanger JP, *et al.* Prognostic value of admission glucose in nondiabetic patients with myocardial infarction. Am Heart J. 2004; 148: 399-404. PMid:15389225 http://dx.doi.org/10.1016/j.ahj.2004.04.007

[23] Wahab NN, Cowden EA, Pearce NJ, *et al.* Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? J Am Coll Cardiol. 2002; 40: 1748-1754. http://dx.doi.org/10.1016/S0735-1097(02)02483-X

[24] Kosiborod M, Rathore SS, Inzucchi SE, *et al*. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation. 2005; 111: 3078-3086. PMid:15939812 http://dx.doi.org/10.1161/CIRCULATIONAHA.104.517839

[25] Capes SE, Hunt D, Malmberg K, *et al*. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic

overview. Stroke. 2001; 32: 242-2432. http://dx.doi.org/10.1161/hs1001.096194

[26] Bruno A, Levine SR, Frankel MR, *et al*. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology. 2002; 59: 669-674. PMid:12221155 http://dx.doi.org/10.1212/WNL.59.5.669

[27] Finney SJ, Zekveld C, Elia A, *et al*. Glucose control and mortality in critically ill patients. JAMA. 2003; 290: 2041-2047. PMid:14559958 http://dx.doi.org/10.1001/jama.290.15.2041

[28] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003; 78: 1471-1478. PMid:14661676 http://dx.doi.org/10.4065/78.12.1471

[29] Furnary AP, Zerr KJ, Grunkemeier GL, *et al.* Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999; 67: 352-360. http://dx.doi.org/10.1016/S0003-4975(99)00014-4

[30] Golden SH, Peart-Vigilance C, Kao WH, *et al.* Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care. 1999; 22: 1408-1414. PMid:10480501 http://dx.doi.org/10.2337/diacare.22.9.1408

[31] Laird AM, Miller PR, Kilgo PD, *et al*. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma. 2004; 56: 1058-1062. PMid:15179246 http://dx.doi.org/10.1097/01.TA.0000123267.39011.9F

[32] Vogelzang M, Nijboer JM, van der Horst IC, *et al*. Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. J Trauma. 2006; 60: 873-877. PMid:16612311 http://dx.doi.org/10.1097/01.ta.0000195715.63978.80

[33] Sung J, Bochicchio GV, Joshi M, *et al*. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma. 2005; 59: 80-83. PMid:16096543 http://dx.doi.org/10.1097/01.TA.0000171452.96585.84

[34] Bochicchio GV, Sung J, Joshi M, *et al*. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma. 2005; 58: 921-924. PMid:15920404 http://dx.doi.org/10.1097/01.TA.0000162141.26392.07

[35] Van den Berghe G, Schoonheydt K, Becx P, *et al*. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005; 64: 1348-1353. PMid:15851721 http://dx.doi.org/10.1212/01.WNL.0000158442.08857.FC

[36] McGirt MJ, Woodworth GF, Brooke BS, *et al*. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. Neurosurgery. 2006; 58(6): 1066-1073. PMid:16723885 http://dx.doi.org/10.1227/01.NEU.0000215887.59922.36

[37] Newton JD, Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalisation for heart failure. Heart. 2006; 92: 1441-1446. PMid:16621876 http://dx.doi.org/10.1136/hrt.2005.080895

[38] Barsheshet A, Garty M, Grossman E, *et al.* Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. Arch Intern Med. 2006; 166: 1613-1619. PMid:16908794 http://dx.doi.org/10.1001/archinte.166.15.1613

[39] Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. J Pediatr. 2005; 146: 30-34. PMid:15644818 http://dx.doi.org/10.1016/j.jpeds.2004.08.076

[40] Baker EH, Janaway CH, Philips BJ, *et al*. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006; 61: 284-289. PMid:16449265 http://dx.doi.org/10.1136/thx.2005.051029

[41] Kao LS, Morris BH, Lally KP, *et al*. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol. 2006; 26: 730-736. PMid:16929344 http://dx.doi.org/10.1038/sj.jp.7211593

[42] The ACCP/SCCM Consensus Conference Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992; 101: 1644-1655. http://dx.doi.org/10.1378/chest.101.6.1644

[43] Bellomo R, Ronco C, Kellum JA, *et al*. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004; 8: R204-R212. PMid:15312219 http://dx.doi.org/10.1186/cc2872

[44] Ascione R, Rogers CA, Rajakaruna C, *et al.* Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. Circulation. 2008; 118(2): 113-23. PMid:18591441 http://dx.doi.org/10.1161/CIRCULATIONAHA.107.706416

[45] Hudson CC, Welsby IJ, Phillips-Bute B, *et al*. Glycosylated hemoglobin levels and outcome in non-diabetic cardiac surgery patients. Can J Anaesth. 2010; 57(6): 565-72. http://dx.doi.org/10.1007/s12630-010-9294-4

[46] Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999; 21: 69-78. http://dx.doi.org/10.1097/00075197-199901000-00012

[47] McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycaemia. Crit Care Clin. 2001; 17: 107-124. http://dx.doi.org/10.1016/S0749-0704(05)70154-8

[48] Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. Am J Méd. 1995; 98: 75-84. http://dx.doi.org/10.1016/S0002-9343(99)80083-7

[49] Pittas AG, Siegel RD, Lau J. Insulin therapy and in-hospital mortality in critically ill patients: systematic review and meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr. 2006; 30: 164-172. PMid:16517961 http://dx.doi.org/10.1177/0148607106030002164

[50] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2009; 300(8): 933-944. PMid:18728267 http://dx.doi.org/10.1001/jama.300.8.933

[51] The NICE-SUGAR study investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009; 360(13): 1283-97. PMid:19318384 http://dx.doi.org/10.1056/NEJMoa0810625

[52] Whitcomb BW, Pradhan EK, Pittas AG, *et al*. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med. 2005; 33: 2772-2777. PMid:16352959 http://dx.doi.org/10.1097/01.CCM.0000189741.44071.25