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Influence on prognosis and prevalence of stress hyperglycemia in a cohort of patients with acute coronary syndrome

Prevalência e influência da hiperglicemia de estresse no prognóstico em uma coorte de pacientes com síndrome coronariana aguda

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ABSTRACT

Objective: To demonstrate the prevalence of stress hyperglycemia in a cohort of patients with acute coronary syndrome and to determine the correlation of stress hyperglycemia with death, heart failure and/or left ventricular systolic dysfunction during the intrahospital phase.

Methods: A prospective initial cohort study of hospitalized patients with acute coronary syndrome with or without ST segment elevation. The groups were compared to demonstrate the correlation between stress hyperglycemia and cardiovascular events. The chi-square test or Fisher's exact test and student's t-test were used to compare the groups with and without stress hyperglycemia. The variables with $p < 0.20$ in the univariate analysis were submitted to logistic regression.

Results: In total, 363 patients with an average age of 12.45 ± 62.06 were studied. There was a predominance of males

(64.2%). In total, 96 patients (26.4%) presented with stress hyperglycemia. There were no differences between the groups with or without stress hyperglycemia. The area under the ROC curve was 0.67 for the relationship between stress hyperglycemia and the composite outcome heart failure, left ventricular systolic dysfunction or death at the end of the hospital admission. The ROC curve proved that stress hyperglycemia was the predictor of the composite outcome (death, heart failure and/or ventricular dysfunction). The multivariate analysis did not indicate age, stress hyperglycemia or admission heart rate as risk factors.

Conclusion: Stress hyperglycemia was common in the studied sample. In the univariate analysis, the presence of stress hyperglycemia was associated with such events as death, heart failure and/or intrahospital ventricular dysfunction in patients with acute coronary syndrome.

Keywords: Hyperglycemia; Acute coronary syndrome; Prognosis

This study was conducted at the Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense - UFF - Niterói (RJ), Brazil.

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death and disability in numerous countries.⁽¹⁾ The association between hyperglycemia and cardiovascular disease has been well-described for a long time.^(2,3) The leading cause of hospital admissions for patients with diabetes mellitus (DM) is cardiovascular disease, and it must be stressed that acute myocardial infarction (AMI) and cerebrovascular accident (CVA) are the main causes of death in diabetic patients.⁽⁴⁾

Hyperglycemia is a common finding during the admission of patients with acute coronary syndrome and is also a powerful predictor of survival, increasing the risk of immediate and long-term complications.⁽⁵⁾ Epidemiological studies

demonstrate that the relative risk of intrahospital death among patients with acute coronary syndrome (ACS) who were unaware they had DM and/or hyperglycemia at the time of the admission was 3.9 times higher than that of nondiabetics or healthy individuals.⁽⁶⁾

This presence of hyperglycemia upon hospital admission in individuals with ACS who did not report DM is known as stress hyperglycemia (SH) because it is attributable to the adrenergic stimulation resulting from the stress associated with the myocardial ischemic event. The clinical importance of SM has been recognized not only because it indicates a condition of lower pancreatic reserve (and therefore glycemic metabolism changes) but also because it is associated with worse AMI outcomes for diabetic patients compared with nondiabetic patients.⁽⁷⁾

Stress hyperglycemia (SH) is present in 25% to 50% of patients admitted with ACS. SH is associated with the risk of intrahospital complications and is a marker of worse prognosis for such outcomes as mortality, heart failure (HF) and cardiogenic shock.⁽⁸⁾ At the time of the AMI, hyperglycemia may be an important risk factor that is potentially modifiable.⁽⁹⁻¹¹⁾

In view of such observations, this article aimed to describe the prevalence of SH in patients who were admitted with ACS and to analyze its correlation with death, HF and/or left ventricular systolic dysfunction (LVSD) in the sample studied during the intrahospital phase.

METHODS

The present study consisted of a prospective cohort composed of inpatients with ACS with or without ST-segment elevation. The studied sample was part of the project, Cardiovascular risk factors and genetic markers in acute coronary syndromes in the population of Niterói (RJ), which is linked to the Faculdade de Medicina da Universidade Federal Fluminense. The information analyzed in this study was collected from the initial study's database.⁽¹²⁾

All of the patients included in the study read and signed an informed consent form. The study was approved by the Research Ethics Committee of the institution under protocol number 59/03.

The patients were selected and defined according to the following inclusion criteria: admission into the emergency unit within 72 hours after the onset of the symptoms; initial diagnosis of ACS with or without ST-segment elevation; and clinical follow-up throughout the entire hospitalization period. The sample size was determined by the number of patients who were in the study for the

predetermined period, which was the 12 consecutive months between June 2004 and June 2005. The cohort of 363 patients was created by excluding from the initial sample 410 patients those who had a previous history of HF, as determined according to the Boston criteria. The presence of diabetes mellitus was not a criterion for exclusion.

SH in the acute phase of ACS was defined as blood glucose levels greater than or equal to 140 mg/dL without previous reports of DM.^(6,7) In the present study, blood glucose levels were obtained upon the patients' admission to the emergency unit, even in the absence of fasting.

The main outcome of the study consisted of death from general causes, the presence of HF based on the Boston criteria and/or LVSD detected by transthoracic echocardiography until the end of hospitalization.

Statistical analysis

The data are expressed as percentages, means and standard deviation. The patients were categorized in to the following groups: Group 1: patients with outcomes of HF and death; Group 2: patients without these outcomes.

The data were analyzed using student's t-test, the chi-square test or Fisher's exact test. To analyze the sensitivity and specificity of the hypothesis, a receiving operating characteristic (ROC) curve was built to assess the relationship between SH observed upon admission and the outcomes. Variables with $p < 0.20$ were included in the logistic regression, and those with values of $p < 0.05$ were retained in the model. The Statistical Package for the Social Sciences Version 13.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

In total, the study included 363 patients diagnosed with ACS with an average age of 62.06 ± 12.45 years and a predominance of males (64.2%). Among the general characteristics of the studied sample, the most prevalent comorbidities were hypertension (76.6%), dyslipidemia (89.2%) and a history of CAD in first-degree relatives (43.5%).

Stress hyperglycemia was observed in 96 patients (26.4%). In the comparison of groups with and without SH, there was no significant difference between the variables used (Table 1). There was a statistically significant difference between the groups regarding mortality ($p < 0.001$); 21% of the patients with SH died during hospitalization compared with 3% of the patients without SH. Patients without HE had a 1.24 times lower

Table 1 - Comparison between groups with or without stress hyperglycemia

Variables	Presence of SH	Absence of SH	p value
Age	62.5 ± 11.0	61.9 ± 13.0	0.16
Gender			
Male	35 (39.3)	95 (34.7)	0.19
Female	54 (60.7)	179 (65.3)	
Previous CAD	36 (40.4)	90 (32.9)	0.30
Previous LVD	0 (0.0)	0 (0.0)	1.00
Smoking	28 (31.5)	91 (33.2)	0.28
Chronic renal failure	4 (4.5)	7 (2.6)	0.70
Physical activity	13 (14.6)	38 (13.9)	0.67
Hypertension	68 (76.5)	192 (70.1)	0.22
Dyslipidemia	85 (95.5)	223 (81.4)	0.84
Acute coronary syndrome			
AMI with STE	34 (38.2)	111 (40.5)	0.51
UA/AMI without STE	55 (61.8)	163 (59.5)	0.62
Admission HR	85.6 ± 22.8	80.6 ± 18.5	0.31
Admission BP	152.7 ± 36.4	142.5 ± 32.5	0.42
Admission creatinine	0.82 ± 1.22	0.75 ± 0.92	0.42
Admission blood sugar levels	152.7 ± 36.4	121.84 ± 47.45	0.03
HR or LVD	43 (44.8)	74 (27.7)	0.53
Mortality	20 (21.0)	8 (3.0)	<0.0001
Composite outcome	63 (65.2)	82 (30.7)	<0.0001

SH - stress hyperglycemia; CAD - coronary arterial disease; LVD - left ventricular dysfunction; AMI with STE - acute myocardium infarction with ST segment elevation; UA - unstable angina; AMI without STE - acute myocardium infarction without ST segment elevation; HR - heart rate; BP - blood pressure; HF - heart failure; LVSD - left ventricular systolic dysfunction. The results are expressed as the mean ± standard deviation, numbers and percentage.

risk of death during the hospitalization period compared with patients with SH (95% confidence interval [95% CI]=1.12-1.36).

When analyzing the clinical data, we found that 117 (32.2%) patients progressed to death and/or developed HF and/or left ventricular systolic dysfunction (LVSD) during hospitalization. A bivariate analysis of the two groups revealed statistically significant differences: the group with outcomes was older ($p<0.001$), had a higher proportion of female patients ($p=0.04$) and had a higher heart rate (HR) on admission ($p=0.02$) compared with the group without the target outcomes (Table 2).

The area under the ROC curve was 0.67, showing that SH predicted the outcomes of HF, LVSD or death. In the multivariate logistic regression analysis, although the variables age (95% CI=0.27 - 1.02; $p=0.04$) and HR on admission (95% CI=1.02 - 4.43; $p=0.4$) showed a significant (lower than 0.05) association between the composite outcome and the respective variables lower, the confidence interval was wide and included the value 1. Thus, it was not possible to prove this association or an association with SH, which showed a wide confidence interval without statistical significance (95% CI=0.76-2.63; $p=0.26$) (Table 3, Figure 1).

Table 2 - Comparison between groups with and without outcomes

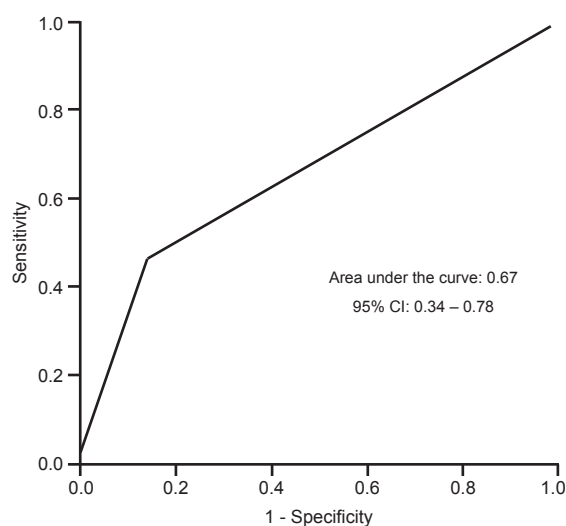
Variables	N (%) General sample	N (%) Presence of outcome	N (%) Absence of outcome	p value
Age	62.06 ± 12.45	65.49 ± 13.05	60.30 ± 11.78	0.001
Gender				
Female	130 (35.8)	50 (40.7)	80 (33.3)	0.04
Male	233 (64.2)	73 (59.3)	160 (66.7)	
BMI	24.77 ± 6.37	25.64 ± 6.18	26.54 ± 5.68	0.32
Hypertension	278 (76.6)	88 (71.5)	172 (71.7)	0.11
Diabetes mellitus	96 (26.4)	35 (28.5)	61 (25.4)	0.19
Dyslipidemia	324 (89.2)	102 (82.9)	206 (85.8)	0.75
Physical activity	51 (14.0)	17 (13.8)	34 (14.2)	0.84
Smoking	119 (32.8)	31 (25.2)	88 (36.7)	0.21
Chronic renal failure	11 (3.0)	3 (2.4)	8 (3.3)	0.48
History of first degree CAD	158 (43.5)	55 (44.7)	103 (42.9)	0.41
Previous CAD	126 (34.7)	40 (30.9)	88 (36.7)	0.28
Previous LVD	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Admission HR	84.5 ± 18.7	96.2 ± 15.6	89.4 ± 14.8	0.02
Admission hyperglycemia	128.3 ± 64.6	177.6 ± 78.4	123.1 ± 63.9	<0.0001

BMI - body mass index; SH - stress hyperglycemia; CAD - coronary arterial disease. The results are expressed as the mean ± standard deviation, numbers and percentage.

Table 3 - Risk factors associated with the composite outcome in the multivariate analysis of logistic regression

Variables	OR	95% CI	p value
Age	0.52	0.27-1.02	0.04
Admission HR	2.13	1.02-4.43	0.04
Stress hyperglycemia	1.41	0.76-2.63	0.26

CI - confidence interval; HR - heart rate.

**Figure 1** - ROC curve for the analysis of the correlation between stress hyperglycemia and the composite outcome (heart failure, left ventricular systolic dysfunction or death) in patients with acute coronary syndrome. CI - confidence interval.

DISCUSSION

In the present study, the prevalence of SH upon admission was 24.5%. The DM did not influence the between-groups analysis, and the presence of SH was shown to predict the outcomes of death, HF or LVSD during the hospitalization period.

Numerous studies have indicated that SH should be a common marker in patients with ACS and is an important risk factor for intrahospital complications.^(5,8) Although the exact cutoff point for SH has not been defined to date, its prevalence in epidemiological studies varies from 25% to 50% of patients admitted with ACS.^(8,13) The present study presents similar prevalence values.

In a study by Marfella et al.,⁽¹⁴⁾ SH was observed in 31 (29%) patients. Nordin et al.,⁽¹⁵⁾ in a retrospective analysis of patients admitted with ACS, observed a 38% prevalence of SH. These findings show variability in prevalence, and no exact definition has been posited on the basis of ethnic specificities or risk groups studied. Unlike the cited studies, the present study found no significant differences in the selected variables between the groups with and without SH.

Several studies demonstrate an association between hyperglycemia and death in populations with ACS. In the CREATE-ECLA study,⁽¹⁶⁾ patients with AMI with ST-segment elevation had a mortality rate of 6.6% within the first 30 days in the control group, whereas in the group with SH, the mortality rate was 14%. In the HI-5 study,⁽¹⁷⁾ mortality was significantly higher in the group with average blood glucose levels greater than or equal to 144 mg/dL.

Suleiman et al.⁽¹⁸⁾ observed in a cohort of 735 nondiabetic patients with AMI that the blood glucose levels on admission were correlated with higher mortality in the first 30 days. Svensson et al.⁽¹⁹⁾ demonstrated that patients with blood glucose levels greater than or equal to 120 mg/dL had 46% higher mortality compared with patients whose blood glucose levels were between 56 and 119 mg/dL. In the present sample, mortality progressed more sharply: 21% of patients who were admitted with SH progressed to death compared with only 3% of the group with normal blood glucose levels.

The differential impact of SH on the outcome of patients with ACS has been assessed by several researchers. Specifically, SH appears to be a strong indicator of adverse effects. Although the pathophysiological mechanisms are not yet fully understood, there are several possible explanations. It is possible that a greater degree of stress is necessary to produce a similar degree of hyperglycemia in

patients without DM than in those with DM.⁽²⁰⁾

The benefits of strict control of blood sugar levels in critical patients have been demonstrated and include reduced rates of organ dysfunction and mortality with the maintenance of blood glucose levels between 80 and 110 mg/dL instead of the old target, which was between 180 and 200 mg/dL. The benefits seem to be related not only to lower blood glucose levels but also to the anti-inflammatory effects of insulin, which reduce the production of substances related to oxidative stress and lower glucotoxicity.⁽²¹⁾

The sample size is one of the limitations of this study; a greater number of patients is needed for more reliable analyses. The inclusion of a greater number of patients could have changed the results of the multivariate analysis, making the association between SH and the outcome significant. Another important point is the echocardiographic diagnosis of LVSD, which was performed by different examiners. Echocardiography is known to be an examiner-dependent method; therefore, its findings are influenced by the number of examiners used. Finally, the present study is clearly subject to confounding factors when patients with DM are not properly excluded.

CONCLUSION

The SH prevalence found in this sample is similar that found in other studies. In the univariate analysis, SH was associated with such events as death, HF and LVSD during the intrahospital follow-up period.

RESUMO

Objetivo: Demonstrar a prevalência da hiperglicemia de estresse em coorte de pacientes com síndrome coronariana aguda e a correlação com óbito, insuficiência cardíaca e/ou disfunção ventricular esquerda sistólica, na fase intra-hospitalar.

Métodos: Estudo de coorte prospectiva inicial constituída por pacientes internados com síndrome coronariana aguda, com ou sem supradesnívelamento do segmento ST. Foram comparados os grupos para demonstrar a correlação entre hiperglicemia de estresse e eventos cardiovasculares. Na comparação entre os grupos com e sem hiperglicemia de estresse, foram usados o teste do qui-quadrado ou exato de Fisher, e o teste *t* de *student*. As variáveis com valor de $p < 0,20$ na análise univariada foram submetidas à regressão logística variáveis.

Resultados: Foram estudados 363 pacientes com média etária de $62,06 \pm 12,45$ anos, com predomínio do gênero masculino (64,2%). O total de 96 pacientes (26,4%) apresentou hiperglicemia de estresse. Não houve diferenças entre os grupos com ou

sem hiperglicemia de estresse. A área sobre a curva ROC foi de 0,67 para relação entre a hiperglicemia de estresse e o desfecho composto insuficiência cardíaca, disfunção sistólica de ventrículo esquerdo ou óbito ao fim da internação. A curva ROC mostrou ser a hiperglicemia de estresse fator preditivo do desfecho composto (óbito, insuficiência cardíaca e/ou disfunção ventricular). A análise multivariada não apontou fator de risco a idade, hiperglicemia de estresse ou frequência cardíaca de admissão.

Conclusão: A hiperglicemia de estresse na amostra estudada foi frequente. Sua presença associou-se, na análise univariada, com eventos como óbito, insuficiência cardíaca e/ou disfunção ventricular na fase intra-hospitalar, em pacientes com síndrome coronariana aguda.

Descritores: Hiperglicemia; Síndrome coronariana aguda; Prognóstico

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