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Original article

Blood Glucose in Acute Coronary Syndromes. How Low Should You Go?

Hélia Martins,* Sílvia Monteiro, Francisco Gonçalves, Pedro Monteiro, and Mariano Pêgo

Departamento de Cardiologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

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ABSTRACT

Introduction and objectives: Hyperglycemia at admission seems to identify a subgroup of patients with acute coronary syndromes with poorer outcome. The aim of this study was to evaluate the impact of the glycemic variation during hospitalization in long-term mortality in nondiabetic patients.
Methods: Retrospective study of 2043 consecutive patients without known diabetes mellitus admitted for acute coronary syndrome in a single coronary care unit from May 2007 through August 2013. The population was divided in quartiles regarding glycemia at admission (≤ 90 mg/dL, n = 374; 90-140 mg/dL, n = 1307; 141-180 mg/dL, n = 230; ≥ 181 mg/dL, n = 111) and the mortality rate quantified for patients with glycemic variation above/below the mean for their respective quartile. The median follow-up was about 1200 days.
Results: The all-cause mortality during follow-up was significantly and successively higher in the upper quartiles (9.1%, 9.7%, 13.5% and 18.9%; *P* = .007). Multivariate regression analysis showed that hyperglycemia at admission (≥ 181 mg/dL) was a strong independent predictor of mortality during follow-up (hazard ratio = 1.74; 95% confidence interval, 1.07-2.8; *P* = .027). In the fourth quartile (≥ 181 mg/dL), the mortality is higher in patients with higher variations of glycemia (37.5% vs 8.5%; *P* < .001).
Conclusions: Hyperglycemia at admission is a predictor of all-cause mortality in our population. The mortality is higher in patients with higher glycemic variations. More studies are needed to confirm these data.

Glucemia en los síndromes coronarios agudos. ¿Hasta qué nivel debe reducirse?

Palabras clave:
Síndrome coronario agudo
Alteración del metabolismo de la glucosa
Variación glucémica
Hiperglucemia de estrés

RESUMEN

Introducción y objetivos: La hiperglucemia al ingreso parece identificar a un subgrupo de pacientes con síndromes coronarios agudos que muestran una peor evolución clínica. El objetivo de este estudio es evaluar la influencia de la variación de la glucemia durante la hospitalización en la mortalidad a largo plazo de los pacientes no diabéticos.
Métodos: Estudio retrospectivo de 2.043 pacientes consecutivos sin diabetes mellitus conocida que ingresaron por un síndrome coronario agudo en una misma unidad coronaria entre mayo de 2007 y agosto de 2013. La población se dividió en cuartiles en función de los valores de glucemia al ingreso (≤ 90 mg/dl, n = 374; 90-140 mg/dl, n = 1.307; 141-180 mg/dl, n = 230; ≥ 181 mg/dl, n = 111) y se determinó la tasa de mortalidad de los pacientes con variaciones de la glucemia por encima o por debajo de la media de su respectivo cuartil. La mediana de seguimiento fue de aproximadamente 1.200 días.
Resultados: La mortalidad por cualquier causa durante el seguimiento fue sucesiva y significativamente mayor en los cuartiles superiores (el 9,1, el 9,7, el 13,5 y el 18,9%; p = 0,007). El análisis de regresión multivariable puso de manifiesto que la hiperglucemia al ingreso (≥ 181 mg/dl) es un potente factor independiente predictivo de la mortalidad durante el seguimiento (*hazard ratio* = 1,74; intervalo de confianza del 95%, 1,07-2,8; p = 0,027). En el cuarto cuartil (≥ 181 mg/dl), la mortalidad fue superior entre los pacientes con mayores variaciones de la glucemia (el 37,5 frente al 8,5%; p < 0,001).
Conclusiones: La hiperglucemia al ingreso es un factor predictivo de la mortalidad por cualquier causa en nuestra población. La mortalidad es más elevada entre los pacientes con mayores variaciones de la glucemia. Se necesitan más estudios para confirmar estos datos.

* Corresponding author: Departamento de Cardiologia, Centro Hospitalar e Universitário de Coimbra, Praceta Mota Pinto, 3000-075 Coimbra, Portugal.
E-mail address: heliafortunamartins@gmail.com (H. Martins).

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Abbreviations

ACS: acute coronary syndrome

INTRODUCTION

The mortality and morbidity of acute coronary syndrome (ACS) remains high despite all development and investment in prevention, diagnosis, and treatment. Hyperglycemia at admission is a known predictor of a worse outcome in diabetic and nondiabetic patients[1,2] and the role of an intensive glycemic control in the setting of ACS has been discussed. The most recent European guidelines on ST-segment elevation myocardial infarction[3] suggest a "strict, but not too strict" glucose control to avoid hypoglycemia (blood glycemia $\leq$ 198 mg/dL [$\leq$ 11 mmol/L]) and the 2013 American College of Cardiology Foundation/American Heart Association[4] guidelines suggest the maintenance of blood glucose levels $<$ 180 mg/dL ($\leq$ 10 mol/L), both independently of a previous diagnosis of diabetes mellitus.

In nondiabetic patients, several studies have demonstrated that stress hyperglycemia has a negative predictive value regarding mortality and morbidity.[2,5–10] According to the work of Capes and coworkers, patients with glucose concentrations between 110 mg/dL and 143 mg/dL had a 3.9-fold higher risk of death compared to patients with lower glucose concentrations. Glucose values between 144 mg/dL and 180 mg/dL were associated with a 3-fold higher risk of heart failure or cardiogenic shock.[8] Besides the hyperglycemia at admission, the failure of glucose levels to decrease in the first 24 h after ACS, a higher first fasting glucose measurement, and glycemic variation also seems to predict higher mortality in nondiabetic patients.[11–13]

The aim of this study was to evaluate the impact of glycemic variation during hospitalization on long-term mortality in nondiabetic patients, assuming active control of glycemia $\geq$ 180 mg/dL and aiming for normoglycemia (90-140 mg/dL).

METHODS

Patient Population and Protocol

Retrospective study of 2043 consecutive patients without known diabetes mellitus admitted for ACS in a single coronary care unit from May 2007 through August 2013. Patients $>$ 18 years with any type of ACS were included. Patients previously diagnosed with diabetes mellitus were excluded, as well as all patients medicated with antidiabetic oral agents or insulin. Readmissions to the same coronary care unit were not considered for statistic analysis. In-hospital deaths were excluded (3.9% of the initial population of nondiabetics admitted for ACS).

The diagnosis of ACS was based on clinical, electrocardiographic and analytical criteria, according to available guidelines at the time of hospital admission. Twenty-one patients (1% of total population) were lost to follow-up.

The population was divided in quartiles regarding glycemia at admission (quartile 1 [Q1], $\leq$ 90, n = 374; quartile 2 [Q2], 90-140, n = 1307; quartile 3 [Q3], 141-180, n = 230; quartile 4 [Q4], $\geq$ 181, n = 111). The glycemic variation was calculated for each patient from the glycemia at admission and the minimum value of glycemia during hospitalization. The mean (mg/dL) of the glycemic variations for each quartile was calculated (Q1, 4 mg/dL; Q2, 21 mg/dL; Q3, 58 mg/dl; Q4, 130 mg/dL) and patient mortality was classified according to glycemic variation below or above the mean for their respective quartile: Q1, 216/158; Q2, 722/585; Q3, 93/137, and Q4, 71/40, respectively.

Data Collection and Endpoint

Clinical, analytical, and demographic data were retrospectively extracted using dedicated software used in the coronary care unit. Since data is systematically registered for every patient, there were no missing data for the analyzed parameters. The oral glucose tolerance test was performed on day 3 or 4 after admission. To standardize glucose determinations, only venous plasma measurements were considered.

Primary endpoint was all-cause mortality rate of patients above/below the mean of glycemia variation within their quartile (based on glycemia at admission).

Statistical Analysis

Continuous data were normally distributed as evaluated with the Shapiro-Wilk test, and therefore is presented as mean (standard deviation). Dichotomous variables are presented as percentages. Comparison of data between groups was made using one-way analysis of variance for continuous data, and chi-square (or Fisher exact test, as appropriate) for dichotomous data.

All variables with a significant P-value $\leq$ .10 for all-cause mortality were tested using a multivariate Cox-regression test, with all the variables in the final model reaching a P-value $<$ .05. Relevant variables with significant between-groups differences in univariate analysis (age, type of ACS, heart rate, admission Killip class III/IV, glycemia at admission $\geq$ 181 mg/dL, left ventricular ejection fraction, maximum troponin, minimum hemoglobin, and prior use of acetylsalicylic acid, beta-blockers and statins) were also included in the model to adjust the final analysis for all possible confounders. Survival curves were constructed by the Kaplan-Meier method and were compared using the log rank test.

All analysis was performed with SPSS for Windows, version 20.0 (SPSS Inc.; Chicago, Illinois, United States). A 2-sided P-value $\leq$ .05 was considered statistically significant. The median follow-up was about 1200 days.

RESULTS

The baseline characteristics of the population are presented in Table 1. In our population, mean glycemia level at admission was 83.3 (6.5) mg/dL in Q1, 109.9 (13.2) mg/dL in Q2, 155.6 (10.5) mg/dL in Q3 and 236.5 (66.6) mg/dL in Q4 (P $<$ .001). The minimum fasting glycemia during hospitalization was 79.2 (7.1) mg/dL in Q1, 89.4 (11.4) mg/dL in Q2, 97.3 (18.4) mg/dL in Q3 and 106.4 (29.2) mg/dL in Q4 (P $<$ .001). By quartile, patients were admitted with the following diagnoses: unstable angina (46.6%, 26.9%, 17%, and 9.4%, respectively; P $<$ .001), ST-segment elevation myocardial infarction (40.2%, 40.7%, 41.8%, and 35.8%; no significant difference) and non—ST-segment elevation acute myocardial infarction (12.1%, 30.7%, 48.9%, and 46.2%; P $<$ .001). Distribution by sex was similar between groups but the age was higher in the higher quartiles.

The length of hospitalization (days) was higher in the higher quartiles (3.7 [2.4], 4.2 [2.7], 5.0 [3.0], 5.6 [4.2], P $<$ .001). Regarding clinical parameters, the heart rate (beats/min) was significantly different between groups, with Q3 and Q4 having higher values (71.6 [13.9], 74.3 [14.4], 78.5 [20.5], and 81.7 [20.4], respectively; P $<$ .001) as well as admission Killip class III/IV (0.5%, 1.5%, 8.3%, and 9.2%, respectively; P $<$ .001). The prevalence of cardiovascular risk factors was similar between groups except for previous known