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Hyperglycemia as a prognostic factor for in-hospital complications in ST segment elevation acute myocardial infarction

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ARTICLE INFORMATION

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Acronyms
ACS: Acute coronary syndrome
CVD: cardiovascular disease
FBG: first fasting blood glucose
PCI: percutaneous coronary intervention
STEMI: ST-segment elevation myocardial infarction

ABSTRACT

Introduction: Mortality and complications remains high in acute myocardial infarction (AMI) patients despite newer reperfusion techniques were being introduced. Hyperglycemia has been described in several studies as a risk factor and worse prognosis.

Objectives: To demonstrate the importance of hyperglycemia as a risk factor for in-hospital complications in ST-segment elevation AMI.

Method: Analytical, longitudinal and prospective cohort study, from 2013 to 2017, which included 307 consecutive patients who were admitted to the Intensive Coronary Care Unit of the Hospital Militar Central Dr. Carlos J. Finlay, with an ST-segment elevation AMI diagnosis.

Results: Mean age was 63.8±11.8 years and the male sex prevailed (61.8%). The main risk factors were high blood pressure and smoking. Of all patients, 119 (38.8%) suffered in-hospital complications. Age ≥ 60 years, Killip-Kimball functional class ≥ II, non-performance of percutaneous coronary intervention and hospital stay were independent prognostic factors of adverse events during admission. Fasting hyperglycemia was shown as an independent predictor of complications from binary logistic regression (p=0.0035, β=0.2971).

Conclusions: Hyperglycemia, measured through fasting blood glucose, is an independent predictor of in-hospital complications in patients with ST-segment elevation AMI.

Keywords: Myocardial infarction, Complications, Hyperglycemia

Hiperglucemia como factor pronóstico de complicaciones intrahospitalarias en el infarto agudo de miocardio con supradesnivel del segmento ST

RESUMEN

Introducción: A pesar de la introducción de nuevas técnicas para la reperfusión del vaso en el infarto agudo de miocardio, las complicaciones y la mortalidad en estos pacientes, es elevada. La hiperglucemia se ha descrito en varios trabajos como factor de riesgo y de peor pronóstico.

Objetivo: Demostrar la importancia de la hiperglucemia como factor de riesgo de complicaciones intrahospitalarias del infarto agudo de miocardio con elevación del segmento ST.

Método: Estudio analítico, longitudinal y prospectivo de cohorte, desde 2013 hasta 2017, que incluyó a 307 pacientes consecutivos que ingresaron en la Unidad de Cuidados Coronarios Intensivos del Hospital Militar Central Dr. Carlos J. Finlay, con el diagnóstico de infarto agudo de miocardio con elevación del segmento ST.

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Resultados: La edad media fue de 63,8±11,8 años y predominó el sexo masculino (61,8%). Los principales factores de riesgo fueron la hipertensión arterial y el tabaquismo. Del total de pacientes, 119 (38,8%) sufrieron complicaciones intrahospitalarias. La edad ≥ 60 años, la clase funcional Killip-Kimball ≥ II, la no realización de intervención coronaria percutánea y la estadía hospitalaria, constituyeron factores pronósticos independientes de eventos adversos durante el ingreso. La hiperglucemia en ayunas se mostró como un factor predictor independiente de complicaciones a partir de la regresión logística binaria (p=0,0035, β=0,2971).
Conclusiones: La hiperglucemia, medida a través de la glucemia en ayunas, es un predictor independiente de complicaciones intrahospitalarias en pacientes con infarto agudo de miocardio con elevación del segmento ST.
Palabras clave: Infarto de miocardio, Complicaciones, Hiperglucemia

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, medical care request and hospitalization in adulthood[1]. Ischemic heart disease accounts for 30% of all heart disease; while more than seven million people die each from this disease, accounting for 12.8% of all deaths[1].

When addressing the general consequences of atherosclerotic CVD we may get the feeling that nothing has changed in the last 40 years, but this is not true; the epidemic has been very dynamic and is influenced by changes in cardiovascular risk factors and increased possibilities of specific interventions for prevention and treatment. All this produces increases and decreases in cardiovascular morbidity and mortality over short periods, with great variability throughout the world, including developing countries, where the highest percentage of events currently occurs. Concerning to model, magnitude and time periods, the epidemic dynamics markedly vary in different parts of the world[2]. The burden is high in Europe: LCA is the leading cause of premature death among women, accounting for 42% of all deaths among European women under 75, and 38% of all deaths among men in the same age range[3].

Cardiovascular diseases appear as the first cause of death in Cuba (241.6 per 100.000 inhabitants) according to data from the 2017 Health Statistical Yearbook. Among them, ischemic cardiopathy ranks first (156.7 per 100.000 inhabitants)[4]. Hospital mortality of patients with ST-segment elevation AMI (STEMI), unselected in the national registries of European countries varies between 6 and 14%[5].

Several recent studies have highlighted a decrease in acute and long-term mortality after STEMI, in parallel with an increase in reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy and secondary prevention treatments[6-8]. Yet, patient mortality remains high with nearly 12% in six months and higher rates in patients at higher risk [6], justifying continued efforts to improve quality of care, adherence to guidelines and research.

Some of the independent predictors of early death in patients with STEMI include age, Killip-Kimball class, reperfusion time, cardiac arrest, tachycardia, hypotension, inferior wall STEMI, old infarction, diabetes mellitus, active smoker, kidney failure, and enzyme results[9,10]. While TIMI (Thrombolysis in Myocardial Infarction) scale was particularly developed for patients with STEMI[11], the GRACE scale predicts in-hospital and six-month mortality in patients with acute coronary syndrome (ACS). Risk prediction is an ongoing process that must be repeated during admission and at discharge.

In recent years, a number of studies have focused on investigating the prognostic value of hyperglycemia in ACS, regardless of whether or not patients had diabetes mellitus.[12] Acute or stressful hyperglycemia plays a facilitating role in the development of ACS and accentuates the consequences of cell damage caused by acute myocardial ischemia. Excess free radicals (due to

increased oxidative cellular stress produced by hyperglycemia) lead to increased fibrinopeptide A, factor VII, and activated prothrombin fragments concentrations. Moreover, they increase the degree of endothelial dysfunction, platelet activation/aggregation, and the half-life of the fibrinogen is shortened; which contributes to the development of intravascular thrombosis, typical of ACS. Likewise, acute hyperglycemia produces a significant length-

ening of the QT interval, reduces ischemic preconditioning, increases non-reflux, depresses myocardial contractility and increases local and systemic inflammatory degree. Even in STEMI patients referred to PCI, hyperglycemia also has a worse short-term prognostic significance, regardless of whether they have diabetes. The results of these and other studies allow us to assuredly state that hyperglycemia implies a worse outcome not only in patients with known diabetes, but also in those without a history of diabetes mellitus. Consequently, hyperglycemia has recently been considered as an independent risk factor in the prognostic assessment of patients with ACS[13]. In view of the above, it was decided to carry out the following study, essentially aimed at demonstrating the importance of hyperglycemia as a risk factor for in-hospital complications in patients with STEMI.

METHOD

We conducted an analytical, longitudinal and prospective cohort study of 307 consecutive STEMI patients admitted to the Intensive Coronary Care Unit of the *Hospital Militar Central Dr. Carlos J. Finlay* from September 2013 to January 30, 2017, based on the criteria of the Third Universal Definition of Myocardial infarction[2].

Each patient was assigned to one of the two groups relative to the first fasting blood glucose (FBG) values during the acute ischemic event. A cut-off value of 7.0 mmol/L according to the American Diabetes Association classification using the glucose oxidase method was taken, and those with fasting numbers equal to or greater than 7.0 mmol/L were defined as hyperglycemia, while those with numbers lower than 7.0 mmol/L were defined as normoglycemia[14].

Variables

Clinical and epidemiological variables were prospectively recorded in a digital card for each patient, comprising: age, sex, personal history diabetes mellitus, hypertension, dyslipidemia, smoking, myocardial infarction , stroke and Killip-Kimball class at admission, ECG location of the infarction, reperfusion therapy (fibrinolysis or PCI), hospital stay, in-hospital complications, discharge status (alive or deceased) and FBG values since admission.

Location of the STEMI: anteroseptal, anterolateral, extensive anterior, inferior, inferolateral, lateral and inferoposterior locations were considered, according to electrocardiographic manifestations.

In-hospital complications in STEMI: arrhythmias, postinfarction angina, congestive heart failure, cardiogenic shock, right ventricular infarction, reinfarction, mechanical complications (ventricular septal defect, free wall rupture, papillary muscle rupture), acute pericarditis, cardiorespiratory arrest, neurological and other complications (typical of treatment) were taken into account. Patients were followed during hospitalization to identify the occurrence of in-hospital complications.

Data processing

Data were analyzed using the statistical system STATISTIC version 7.0 (StatSoft, Inc; Oklahoma, United States). Descriptive statistical methods such as frequency distributions, central trend measures (mean and standard deviation) and percentage calculations were used for the processing and presentation of results, as well as for comparison and analysis by control strata. Chi-square or Fisher's exact test were used to evaluate the association between categorical variables; likewise, relative risk (RR) calculation was also used to assess the association between incidence of complications and exposure of interest.

The association between quantitative variables and the development of complications was contrasted by means of the Student t test or analysis of the variance, according to the number of categories from the variable studied. Finally, a multivariate logistic regression analysis was performed in which the probability or opportunity ratio (OR) to present complications adjusted for FBG was calculated, as well as for the variables that were statistically significant and clinically relevant in the univariate analysis. The level of statistical significance was $p<0.05$ with a 95% confidence interval. Results were expressed as percentages and mean values±standard deviation in the form of tables and graphs.

RESULTS

The study included 307 patients, with a mean age of 63.8±11.7 years. The sample included 193 men and 114 women (62.7% and 37.3%, respectively). In both sexes the age group 50 to 70 years was predominant (**Table 1**).

In the distribution of patients according to the main coronary risk factors and personal history, a high prevalence of smoking (65.8%) and hypertension (65.1%) was observed, followed by diabetes mellitus and a history of previous myocardial infarction. It is worth noting that more than half of the sample was included in the group of hyperglycemic patients, representing 52.1%.

With regard to the location of the infarction, 150 cases (48.8%) had inferior wall STEMI and 116 (37.8%) anterior wall STEMI. According to the functional classification observed on arrival at the Emergency Department, 40 patients (13.0%) presented a Killip-Kimball class II or higher. Regarding myocardial reperfusion treatment, 186 patients (60.6%) received fibrinolytic treatment and 79 (25.7%) received PCI. The average hospital stay was 7 days (**Table 1**).

Table 2 shows the incidence of in-hospital complications stratified by discharge status. Of the total number of patients, 119 (38.8%) suffered some complication, being fatal in 15 of them, resulting in a total mortality of 4.9% for this series. Postinfarction angina was the most frequent in-hospital complication (13.0%), followed by cardiogenic shock (4.9%), non-shock heart failure (4.9%) and arrhythmias (4.7%). Cardiogenic shock (p=0.0037), cardiorespiratory arrest (p=0.0004), mechanical complications (p< 0.0001) and neurological complications (p=0.0489) were significantly associated with in-hospital mortality.

Univariate analysis, performed in order to recognize prognostic factors for the occurrence of in-hospital complications, is shown in **table 3**. Only age equal to or greater than 60 years (p=0.0471; RR 2.709 [1.96-3.68]), Killip-Kimball functional classification of equal to or greater than class II (p<0.0001; RR 2.561 [2.06-3.17]), no PCI (p=0.0003); RR 1.693 [1.30-2.17]) and a stay of seven days or longer (p<0,0001; RR 1.971 [1,48-2.57]) were significantly associated with the occurrence of complications during admission. The greatest relative risk was reached by age≥60 years and functional class, compared with all other prognostic factors.

Table 1. Baseline characteristics of patients (n=307).

Variable	Nº	%
Age (mean ± SD)	63.8 ± 11.8	
Risk Factors		
Male	193	62.7
High blood pressure	200	65.1
Smoking	202	65.8
Diabetes mellitus	68	22.1
Dyslipidemia	4	1.3
Previous AMI	56	18.2
Previous stroke	13	4.2
Hyperglycemia	160	52.1
Location of the infarction		
Inferior	150	48.8
Extensive anterior	67	21.8
Anteroseptal	32	10.4
Anterolateral	17	5.5
Lateral	19	6.2
Inferolateral	20	6.5
Inferior	2	0.7
Hospital Criteria		
Killip-Kimball Class ≥ II	40	13.0
Fibrinolysis	186	60.6
PCI	79	25.7
Stay (mean ± SD)	6.97 ± 3.7	

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

In relation to FBG and its association with in-hospital complications (**Figure**), we found that mean blood glucose values differed significantly among the group of patients who presented complications from those who did not (8.51 vs. 8.07 mmol/L; p=0.0318).

Fasting hyperglycemia (**Table 4**) was identified as a prognostic factor from binary logistic regression (p=0.0035; 95% CI; β=0.2971). The Killip-Kimball functional classification, non-performance of PCI and prolonged hospital stay were also predictors of complications. The rest of the variables did not reach a significant level.

Table 2. Incidence of in-hospital complications stratified by discharge status.

Complication	Discharge Status			*p*
	Alive (n=292)	Deceased (n=15)	Total (%)	
Mechanical	**3**	**5**	**8 (2.6)**	**< 0.0001**
Postinfarction angina	39	1	40 (13.0)	0.3939
Pericarditis	10	0	10 (3.3)	0.6013
Right ventricular infarction	5	0	5 (1.6)	0.7771
Cardiogenic shock	**11**	**4**	**15 (4.9)**	**0.0037**
Cardiorespiratory arrest	**5**	**4**	**9 (2.9)**	**0.0004**
Arrhythmias	14	0	14 (4.7)	0.4882
Heart failure	15	0	15 (4.9)	0.4632
Reinfarction	1	0	1 (0.3)	0.9511
Neurological	**0**	**1**	**1 (0.3)**	**0.0489**
Other	1	0	1 (0.3)	0.9511

DISCUSSION

Blood glucose disorders are frequently found in people with STEMI and are closely associated with an increased risk of complications and death after these events in the general and diabetic population[12,13,15-22]. Although diabetes is already considered in recent studies as an equivalent of cardiovascular disease and not just a risk factor, the state of hyperglycemia at the time of admission has been described as an equal or even more important prognostic factor than diabetic history[12,13,15,17,19]. In this connection, most published studies assess the influence of initial blood glucose on the prognosis of patients admitted with ACS. However, some authors had already anticipated the possible determining role of fasting hyperglycemia[18,20].

Table 3. Univariate analysis of clinical and demographic variables stratified by the onset of in-hospital complications.

Characteristics	p	RR CI 95%
Age ≥ 60 years	**0.0471**	**2.709 (1.96-3.68)**
Sex	0.4394	1.123 (0.83-1.50)
High blood pressure	0.1114	1.284 (0.93-1.75)
Smoking	0.7482	0.952 (0.71-1.27)
Diabetes mellitus	0.5058	0.887 (0.62-1.26)
Dyslipidemia	0.1637	1.959 (1.10-3.45)
Previous myocardial infarction	0.9291	1.016 (0.71-1.44)
Previous stroke	0.5761	1.2 (0.66-2.15)
Previous location	0.0892	0.157 (0.12-0.20)
Killip-Kimball Class ≥ II	**< 0.0001**	**2.561 (2.06-3.17)**
Fibrinolysis	0.8287	1.03 (0.78-1.35)
PCI	**0.0003**	**1.693 (1.30-2.17)**
Stay ≥ 7 días	**< 0.0001**	**1.971 (1.48-2.57)**

CI, confidence interval; PCI, percutaneous coronary intervention; RR, relative risk

In the Framingham Heart Study, referenced by Canto *et al*[23], stable or unstable angina pectoris was more common in women while acute myocardial infarction and sudden cardiac death were more common in men. Age and gender differences may be partly due to the protective effect of estrogens; however, women with arteriosclerosis before age 75 may be particularly vulnerable to more severe disease. Men have a higher risk of myocardial infarction than women, and suffer it at a younger age. Even after menopause, although the death rate from heart disease among women increases, it is not as high

as among men. This may explain the predominance of the male sex in our study.

The risk of myocardial infarction for smokers is more than twice that of nonsmokers. Tobacco smoke is the main risk factor for sudden cardiac death and smokers are two-to four-fold more likely to die than nonsmokers, in addition, smokers who suffer a myocardial infarction are more likely to die and that this fatal event occurs suddenly (within the first hour)[17]. This may somehow explain why more than half of the patients studied smoked at the time of the event.

There is evidence that patients with a history of high blood pressure are six times more likely to develop heart failure than those without a history of high blood pressure[6]. The fact that high blood pressure was one of the most frequent risk factors in the sample studied was to be hoped for, considering that left ventricular hypertrophy for a relatively short period of time will lead to three fundamental complications: impairment of ventricular function that may lead to congestive heart failure, increased myocardial oxygen consumption, which stimulates a decrease in the coronary flow reserve, and the appearance of myocardial ischemia without necessarily causing epicardial coronary arteries stenosis; and finally, the appearance of cardiac, supraventricular and ventricular arrhythmias, which may lead to sudden death[6,8].

Univariate analysis of risk factors stratified by the occurrence of complications during hospitalization showed significant association between their occurrence and age≥60 years, functional class Killip-Kimball≥II, non-performance of PCI and stay≥7 days; which coincides with the studies reviewed[6-9].

Several papers describe both fasting and admission hyperglycemia as a risk factor with strong statistical association with in-hospital complications of patients with STEMI. Zhao *et al*[15], in a study of more than 10.000 patients with STEMI in China, divided the sample between known and non-diabetic diabetics. Each of the groups was divided into hypoglycemia, slightly elevated hyperglycemia and very elevated accord-

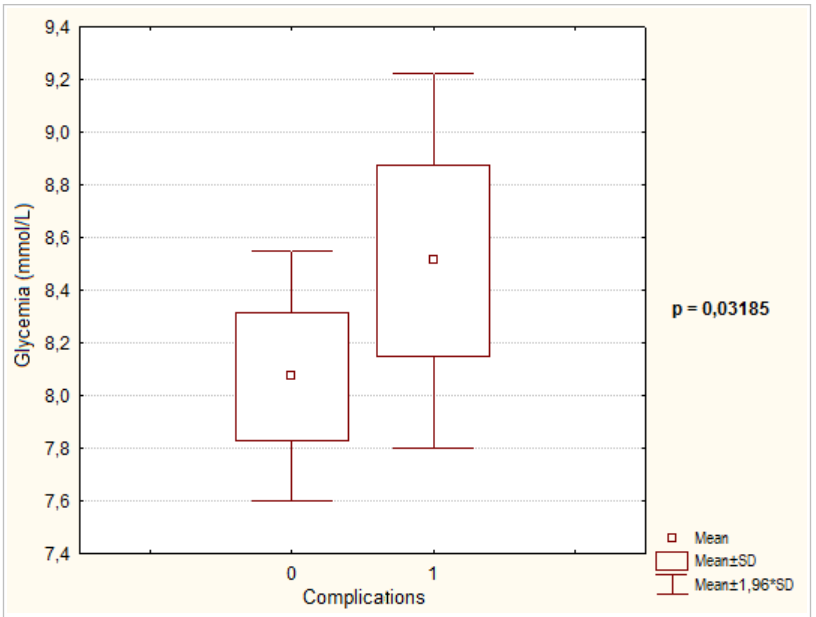

Figure. Comparison of fasting blood glucose averages stratified with the occurrence of in-hospital complications.

Table 4. Multivariate analysis for prognostic factors of in-hospital complications.

Prognostic factors	p	Valor Beta IC 95%
Age	0.2786	0.0645
Sex	0.4715	0.0384
High blood pressure	0.2699	0.0597
Smoking	0.6010	-0.03
Diabetes mellitus	0.0831	-0.1077
Dyslipidemia	0.2272	0.0645
Previous myocardial infarction	0.4812	-0.0379
Previous stroke	0.5899	0.0284
Location	0.4251	-0.0424
Killip-Kimball Class ≥ II	**< 0.0001**	**0.3211**
Fibrinolysis	0.3364	0.0516
Percutaneous coronary intervention	**0.0019**	**0.1707**
Fasting hyperglycemia	**0.0035**	**0.2971**
Stay	**0.0053**	**0.1510**

ing to the blood glucose values at admission. The authors concluded that, in both diabetic and non-diabetic patients, hyperglycemia was significantly associated with in-hospital mortality[15]. On the other hand, a study published in Russia by Karetnikova *et al*[18] enrolled 529 consecutive patients with STEMI, without taking into account the previous diagnosis of diabetes mellitus, who had their blood glucose measured on admission and fasting. They concluded that both admission/fasting hyperglycemia, affects the short and long-term prognosis of patients with STEMI.

In our work, arithmetic means of fasting glycemia were compared with the occurrence of complications and a significant statistical association was found (p=0.0318). These results are consistent with the investigations described above, as well as with the multicenter study carried out in Colombia and Ecuador by Gomez-Arbelaez *et al*[20], which included 439 patients from eight hospitals with the confirmed diagnosis of STEMI, and compared fasting blood glucose values. Furthermore, the glucose tolerance test was included in diabetic patients. Such study, after a three years' follow-up, confirmed the negative short-and medium-term effect of hyperglycemia in these patients.

On the other hand, the multivariate analysis for risk factors associated with in-hospital complications shows that fasting hyperglycemia is an independent predictor of complications from binary logistic regression (p=0.0035, β=0.2971). The functional class Killip-Kimball (p<0.0001, β=0.3211), non-performance of PCI (p=0.0019, β=0.1707) and hospital stay (p= 0.0053, β=0.1510) were also predictors of complications; which coincides with those published by other studies[13,15,16,18-22].

The explanation of why fasting hyperglycemia better predicts the development of complications may be related to several hypotheses. Circadian changes in blood glucose numbers and variability in time since the last intake and the time the patient is admitted with an ACS may encumber initial blood glucose values[24]. However, as these events do not influence it, fasting blood glucose more reliably represents the metabolic state of the patient at that time. In addition, another factor that reinforces the greater importance of FBG, when compared with glucose levels on admission, is the unfavorable outcome of the disease during the first hours of hospital admission (either by the severity of the picture or by a worse therapeutic strategy during the beginning of treatment), which could aggravate the metabolic consequences with higher glycemic figures as the clinical situation worsens.

The results obtained in the present study allow us to consider fasting hyperglycemia as a prognostic factor of in-hospital complications in patients with STEMI. Our results strongly underpin the prognostic importance of diabetes mellitus and hyperglycemia in patients suffering from STEMI.

CONCLUSIONS

Hyperglycemia, measured by fasting blood glucose, is an independent predictor for in-hospital complications in STEMI. Other independent predictors obtained in the study are the functional class Killip-Kimball≥II, non-performance of PCI and prolonged hospital stay.

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