Unrecognized Diabetes and Myocardial Necrosis: Predictors of Hyperglycemia in Myocardial Infarction

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Abstract

Background: Hyperglycemia in the acute phase of myocardial infarction is an important prognostic factor. However, its pathophysiology is not fully understood.

Objective: To analyze simultaneously the correlation between hyperglycemia and biochemical markers related to stress, glucose and lipid metabolism, coagulation, inflammation, and myocardial necrosis.

Methods: Eighty patients with acute myocardial infarction were prospectively included. The following parameters were analyzed: blood glucose; stress hormones (cortisol and norepinephrine); glucose metabolism factors [glycated hemoglobin (HbA1c); insulin]; lipoproteins (total cholesterol, LDL, HDL, minimally modified electronegative LDL, and adiponectin); glycerides (triglycerides, VLDL and fatty acids); coagulation factors (factor VII, fibrinogen, plasminogen activator inhibitor-1); inflammation (high-sensitivity C reactive protein); and myocardial necrosis (CK-MB and troponin). Continuous variables were converted into degrees of relevance using fuzzy logic.

Results: Significant correlation was observed between hyperglycemia and glucose metabolism ($p < 0.001$), lipoproteins ($p = 0.03$), and necrosis factors ($p = 0.03$). In the multivariate analysis, only glucose metabolism (OR = 4.3; CI = 2.1-68.9; and $p < 0.001$) and myocardial necrosis (OR = 22.5; CI = 2-253; and $p = 0.012$) showed independent and significant correlation. For the analysis of the influence of history of diabetes mellitus, a regression model including only patients without diabetes mellitus was developed, and the results did not change. Finally, in the model adjusted for age, gender, and clinical variables (history of diabetes mellitus, hypertension and dyslipidemia), three variables maintained a significant and independent association with hyperglycemia: glucose metabolism (OR = 24.1; CI = 4.8-122.1; and $p < 0.001$), myocardial necrosis (OR = 21.9; CI = 1.3-360.9; and $p = 0.03$), and history of DM (OR = 27; CI = 3.7-195.7; and $p = 0.001$).

Conclusion: Glucose metabolism and myocardial necrosis markers were the best predictors of hyperglycemia in patients with acute myocardial infarction (Arq Bras Cardiol. 2013; 100(5):404-411).

Keywords: Myocardial Infarction; Diabetes Mellitus; Hyperglicemia; Hemoglobin A, Glycosylated.

Introduction

The first study to evaluate the prevalence of glycosuria in patients with acute myocardial infarction (AMI) without diabetes mellitus (DM) was published in 1931[1]. Since then, many other studies have demonstrated the short[2-6] and long-term[7-9] importance of hyperglycemia (HG) in patients with AMI. In addition, blood glucose levels are predictive of ventricular remodeling after AMI[10].

However, there is no consensus in the medical literature regarding the definition of hyperglycemia during acute coronary syndromes, and recent publications suggest that multiple determinations during hospitalization could add prognostic information for this population[11]. There is also a controversy over the intensive treatment of HG; some publications show benefits, whereas others do not[14-16].

Finally, little has been described on the mechanisms involved in the increased mortality related to HG during AMI, with most of the studies correlating HG with only one of the several variables that may explain the elevation in blood glucose levels. Thus, the main objective of this study is to analyze simultaneously, in the same population, blood glucose levels and biochemical markers related to the stress hormone system, glucose and lipid metabolism, coagulation, inflammation, and myocardial necrosis. Part of this study has been published in a congress as an abstract[17].

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Methods

Patients

A total of 80 patients with AMI (mean age of 60.5 years; 81% males) admitted in a coronary care unit of a tertiary-care hospital were prospectively included.

Inclusion criteria: patients with AMI with or without ST-segment elevation with an interval of 24-48 h between the beginning of pain and inclusion in the study.

Exclusion criteria: patients with age < 21 or > 80 years; previous use of corticosteroids; known inflammatory disease; chronic renal failure (creatinine clearance ≤ 60 mL/min); severe neurological disease; hypo- or hyperthyroidism; hemodynamic instability (modified Forester > IIa)[18]; known hematological disease; previous use of anticoagulant drugs; use of fibrinolytic agents during the event studied; or comorbidity with a life expectancy < 6 months.

Laboratory assessments

Blood samples were collected under fasting conditions, 24-48 h prior to the beginning of pain, and the following parameters (and respective reference values) were assessed: glucose (70-100 mg/dL); cortisol (7.3-24.7 μg / dL); norepinephrine (40-268 pg/mL); HbA1c (< 6.1%); insulin (2.3-26.4 μU/mL); nonesterified fatty acid (NEFA) (0.1-0.6 mEq/L); coagulation factor VII (50-150%); and high-sensitivity C reactive protein (hsPCR) (< 5 mg/L). In addition, levels of lipids and myocardial necrosis markers were determined according to the routine protocol for patients with AMI, and the reference values are as follows: total cholesterol (< 200 mg/dL); low-density lipoprotein (LDL) (< 100 mg/dL); high-density lipoprotein (HDL) (> 40 mg/dL for men and > 50 mg/dL for women); very-low-density lipoprotein (VLDL) (no reference value); triglycerides (< 150 mg/dL); MB fraction of creatine phosphokinase (CK-MB) (< 4 ng/mL); and troponin I (< 0.1 ng/mL).

Minimally-modified electronegative LDL [LDL (-)], anti-LDL(-) antibody, plasminogen activator inhibitor (PAI-1), and fibrinogen have no reference values, and their levels were compared between the groups with and without hyperglycemia.

Glucose, total cholesterol, HDL, LDL and triglycerides levels were determined using the enzymatic method in a Cobas Integra 700 analyzer (Roche, Germany). hsCRP was measured using immunoturbidimetric essay (Roche). HbA1c levels were determined in a Hitachi 902 analyzer (Roche). VLDL was calculated. Cortisol and insulin levels were analyzed using AutoDELFIA kits (PerdinElmer, Finland). Norepinephrine levels were measured using high-performance liquid chromatography. LDL (-) and anti-LDL (-) antibodies were determined using ELISA[19]. For NEFA determination, the HR Series NEFA C kit (Wako, Japan) was used. Coagulation factor VII levels were determined using the AMAX kit (Trinity, USA). The LINCOplex Human Disease Panel I was used for simultaneous determinations of adiponectin and PAI-1; SINGLEplex Human Cardiovascular Disease (LINCO, USA) was used to determine fibrinogen levels.

Definitions

DM: known DM, under treatment with diet, oral hypoglycemic agents, or insulin.

AMI: typical rise and gradual fall (troponin), or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: ischemic symptoms, development of pathologic Q waves on electrocardiogram, ECG changes indicative of ischemia (ST-segment elevation or depression), or coronary artery intervention[20].

Hyperglycemia: blood glucose ≥ 108 mg/dL (median blood glucose in our sample). Blood glucose levels ≥ 108 mg/dL have already been demonstrated to be associated with higher mortality in intensive care unit patients[21].

Statistical analysis

Continuous variables are presented as means (± SD) or medians (25-75% percentiles), and categorical variables, as numbers (proportions).

Univariate analysis: nonlinear regression, chi square and Kruskal Wallis tests were used when indicated.

Multivariate analysis: the original values of continuous variables were converted into degrees of relevance using the fuzzy logic principles. Thus, with the ROC curve, sensitivity and specificity values of variables for blood glucose ≥ 108 mg/dL were calculated. Next, cohort values of variables were selected according to the highest sum and highest product of sensitivity and specificity. The degrees of relevance for sum and product were derived from the quotient of the variable value by these cohort values.

Thus, the variables in their original groups can be associated with seven domains:

1 – Stress hormone system: cortisol and norepinephrine.

2 – Glucose metabolism: HbA1c and insulin.

3 – Lipoproteins: total cholesterol, LDL, HDL, LDL (-), anti-LDL (-) antibody, adiponectin.

4 – Glycerides: triglycerides, VLDL (since triglycerides are its major component), and NEFA.

5 – Coagulation: coagulation factor VII, PAI-1, and fibrinogen.

6 – Inflammation: hsCRP.

7 – Myocardial necrosis: CK-MB and troponin.

Weighted means were created based on fuzzy values for the sum and product of sensitivity and specificity. Then, using the ROC curve again, the cut-off value for the seven groups of variables was selected, and these groups were categorized.

Univariate analyses were carried out using the chi square test, and multivariate analysis, using binominal logistic regression.

Differences were considered statistically significant when $p < 0.05$. Data were analyzed using the SPSS statistical program, version 19.0 for Windows.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee, according to the Declaration of Helsinki, and participants gave written informed consent.

Results

Patients' characteristics

Baseline population characteristics, medications and invasive therapy used during hospitalization are shown in Table 1. There is a majority of male patients, as is common in AMI, despite a growing increase of women with acute coronary syndrome. The incidence of risk factors is similar to that reported in the literature. Since our hospital is a tertiary-care hospital, we have a high number of patients with ST-segment elevation AMI. According to our institutional protocol, glycoprotein IIb/IIIa inhibitors are recommended as a second antiplatelet agent in combination with acetylsalicylic acid, and clopidogrel is given only in the follow-up for those undergoing medical therapy or after coronary angioplasty. Thus, if we add the use of clopidogrel to glycoprotein IIb/IIIa inhibitors, we have 96.3% of patients with two antiplatelet agents. Only 16.3% of patients underwent primary angioplasty, since 30% of AMI had ST-segment elevation; thus the procedure was not indicated for the vast majority of them.

Correlation between blood glucose levels and the variables studied – univariate analysis

As shown in Table 2, the variables that showed a statistically significant correlation with blood glucose levels in the univariate analysis were: HbA1c, insulin, LDL, HDL, adiponectin, triglycerides, VLDL, NEFA, and fibrinogen. The positive correlation between blood glucose levels and insulin suggests increased insulin resistance. In fact, the median HOMA-IR[22] was 2.4 (1.1 – 4.5).

The correlation between hyperglycemia and the seven domains (stress hormone system, glucose metabolism, lipoproteins, glycerides, coagulation, inflammation, and myocardial necrosis) is shown in Table 3. There was a positive and significant correlation between hyperglycemia and glucose metabolism and myocardial necrosis, and a negative and significant correlation with lipoproteins.

Correlation between blood glucose levels and the variables studied – multivariate analysis

In the multivariate analysis including the seven domains of variables, only glucose metabolism and myocardial necrosis maintained a significant and independent correlation with hyperglycemia (Table 4).

In order to analyze the influence of history of DM in the results, a second adjusted model including the seven domains was developed, however only with patients without DM. As shown in Table 5, the results remained unchanged.

Finally, a third model adjusted to age, gender and clinical variables associated with blood glucose levels (history of DM, hypertension and dyslipidemia) was developed. In this model (Table 6), three variables showed a significant and independent correlation with hyperglycemia: glucose metabolism, myocardial necrosis and history of DM. This means that during the acute phase of AMI there is a group of patients without known DM who already present with underdiagnosed impaired glucose metabolism.

When only patients without known DM are analyzed, and taking into consideration the HbA1c classification recently published by the American Diabetes Association[23], we found that 3.6% of patients were diabetics (HbA1c $\geq$ 6.5%), 28.6% had glucose intolerance (HbA1c $>$ 5.7% and $<$ 6.4%), and 67.8% were normal (HbA1c $\leq$ 5.6%). There was a significant difference between blood glucose levels during the acute phase of AMI and the three HbA1c classes (Figure 1).

No significant correlation was observed between blood glucose levels and mortality or adverse cardiac events (refractory ischemia, reinfarction, cardiogenic shock, and death), which was a secondary analysis. However, the small number of patients included in the study did not allow any conclusion regarding this issue.

Discussion

The present study comprises two main findings. First, hyperglycemia during the acute phase of AMI, regardless of a previous history of DM, is associated with variables related to glucose metabolism (Hba1c and insulin), thus suggesting that hyperglycemia, initially considered stress-derived, may result from glucose intolerance or DM not diagnosed until AMI. The second important finding is that blood glucose levels are significantly correlated with the AMI extension, as represented by myocardial necrosis markers (CK-MB and troponin).

Hyperglycemia and underdiagnosed glucose intolerance/DM

The fact that a correlation between blood glucose levels and HbA1c was initially found seems to be evident. However, HbA1c represents the mean blood glucose level in the past two months and is minimally affected by the acute hyperglycemia[24]. If the hyperglycemia observed in the initial phase of AMI were merely a response to acute stress, it would have no correlation with glucose metabolism and Hba1c in non-diabetic patients. Thus, one of the probable causes of hyperglycemia in AMI is previously undiagnosed dysglycemia.

Tenerz et al[25] analyzed patients with AMI and no previous diagnosis of DM, and reported that routine tests, such as oral glucose tolerance test (OGTT), or blood glucose determination alone 60 min after the intake of 75g of glucose at the moment of hospital discharge can predict the diagnosis of glucose intolerance within 3 months. Their study corroborates our finding that hyperglycemia during AMI may be associated with a chronic impairment of the glucose metabolism.

Since the 1980's, the role of HbA1c as a prognostic marker in AMI has been studied[26-30]. In the OPTIMAAL study, HbA1c was determined in 2,841 patients with AMI and heart failure. Among these patients, 495 (17%) reported a history of DM. Of the patients without history of DM, increased HbA1c levels correlated with mortality: 13% for patients with HbA1c $<$ 4.95%; 17% for patients with HbA1c between 4.9% and 5.1%, and 22% for patients with HbA1c $>$ 5.1% ($p = 0.02$)[31]. Another study, which also evaluated a population with AMI without history of DM, confirmed DM in 27% of patients, glucose intolerance in 39%, and normal glucose metabolism in 34%[32]. There was no standardization for the diagnosis of abnormal HbA1c levels until 2010, and each author used different cohort values. In the present study, we applied the American Diabetes Association criterion[23] and found 32.2% of patients with impaired glucose metabolism.

Table 1 – Population characteristics (80 patients)*

Age (years)	60.5 ± 10
Male gender, n (%)	65 (81)
Interval between the beginning of pain and/inclusion in the study (hours)	38 ± 68
History of - n (%)	
Diabetes mellitus	24 (30)
Hypertension	62 (77)
Dyslipidemia	44 (55)
Current smoking habit	24 (30)
Acute myocardial infarction	35 (43)
Family history of diabetes mellitus, n (%)	37 (46)
ST-segment elevation infarction, n (%)	24 (30)
Previous infarction, n (%)	31 (39)
CK-MB mass peak (mg/dL)	85 ± 113
Troponin I (ng/mL)	25 ± 38
Medications used at the moment of blood collection, n (%)	
Acetylsalicylic acid	80 (100)
Clopidogrel	25 (31.3)
Glycoprotein IIb/IIIa inhibitors	52 (65)
Betablockers	68 (85)
Angiotensin converting enzyme inhibitor/ Angiotensin II receptor blocker	58 (85)
Statins	57 (71.3)
Unfractionated heparin	14 (17.5)
Enoxaparin	51 (63.8)
Invasive procedures during hospitalization (%)	
Primary angioplasty	13 (16.3)
Non-primary angioplasty	28 (35)
Coronary artery bypass grafting	14 (17.5)

**Continuous variables are expressed as mean ± SD.*

Hyperglycemia and insulin resistance

Insulin, another component of the glucose metabolism, significantly correlated with blood glucose levels, thus suggesting increased insulin resistance, which was demonstrated by the HOMA-IR elevation. This finding is similar to those of Choi et al[33], who demonstrated a significant correlation of glucose tolerance and DM with insulin resistance in patients with AMI. However, this increased insulin resistance may be chronic or related to the acute disease.

In an assessment of insulin resistance and metabolic syndrome in patients with AMI without known DM, blood glucose, insulin (on the 2nd day, 5th day and three months after AMI), HbA1c and OGTT levels (five days and three months after AMI) were determined[25]. Significant elevation of HOMA-IR on the 2nd in relation to the 5th day ($p < 0.001$) was observed; however, no changes were observed between the 5th day and three months. There was a correlation between increased insulin resistance and diabetic patients (86%), those with glucose intolerance (65%), and patients with normal blood glucose (52%), according to the OGTT at three months ($p = 0.004$). This study suggests that the patients who were not aware of having DM or glucose intolerance had higher insulin resistance than patients with normal blood glucose. However, in the first two days, an increase in HOMA-IR occurred, which may be related to the acute phase, associated with stress hormones. This means that the two mechanisms are not mutually exclusive.

Hyperglycemia and myocardial necrosis

AMI extent, as represented by myocardial necrosis markers, was significant and independently related to hyperglycemia in the present study. This relationship had already been described by other authors[34-36]. An association between high blood glucose levels and different variables associated with AMI size, including a high Killip class, low ejection fraction, and increased levels of CPK, CPK-MB, troponin I, pro-BNP

Table 2 – Univariate analysis of the correlation between blood glucose levels and the variables studied

Variables	Determination value (references)	Correlation coefficient (R)	p
Cortisol	14.9 (± 6.5) µg/dL	0.11	0.82
Norepinephrine	334 (236-463) pg/mL	0.14	0.23
HbA1c	5.6 (5.2-6.2) %	0.76	< 0.01
Insulin	8.1 (5.5-14.2) µg/mL	0.36	0.01
Total cholesterol	177 (148-205) mg/dL	0.21	0.32
LDL	109.8 (± 34.6) mg/dL	0.25	0.02
HDL	33 (28-41) mg/dL	0.23	0.02
LDL (-)	7.2 (3.8-19.1) U/L	0.16	0.59
Anti-LDL (-) antibody	0.8 (0.3-1.3) µg/mL	0.14	0.22
Adiponectin	6.9 (4.7-14.8) ng/mL	0.31	0.01
Triglycerides	134 (101-194) mg/dL	0.37	0.01
VLDL	27 (20-38) mg/dL	0.36	0.01
Fatty acids	0.77 (0.6-1) mEq/L	0.33	0.03
Coagulation factor VII	71.9 (18.7) %	0.25	0.17
PAI-1	19.6 (14.5-25.8) pg/mL	0.21	0.91
Fibrinogen	645 (424-940) ng/mL	0.32	0.04
C reactive protein	14.8 (5.2-34.5) mg/L	0.11	0.83
CK MB	35.3 (14.2-102) ng/mL	0.28	0.1
Troponin I	25.6 (2.7-35) ng/mL	0.13	0.75

HbA1c: glycated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LDL (-): minimally modified electronegative LDL; VLDL: very-low-density lipoprotein; PAI-1: plasminogen-1 activator inhibitor; CK-MB: creatine kinase MB.

Table 3 – Univariate analysis – hyperglycemia* and Fuzzy domains

Variables	With hyperglycemia	Without hyperglycemia	p
Hormone system	46.7%	53.3%	0.27
Glucose metabolism	80.5%	19.5%	< 0.01
Lipoproteins	39.5%	60.5%	0.03
Glycerides	57.9%	42.1%	0.06
Coagulation	62.5%	37.5%	0.1
Inflammation	59.2%	40.8%	0.31
Myocardial necrosis	87.5%	12.5%	0.03

**Glucose ≥ 108mg/dL.*

Table 4 – Multivariate analysis – Predictors of hyperglycemia*

Variables	p	OR (95%CI)
Glucose metabolism	< 0.01	4.3 (2.1-68.9)
Myocardial necrosis	0.01	22.5 (2-253)

** Glucose ≥ 108 mg/dL.*

Table 5 – Multivariate analysis – Predictors of hyperglycemia* (excluding patients with history of diabetes mellitus)

Variables	p	OR (95%CI)
Glucose metabolism	0.01	42.6 (4.9-367)
Myocardial necrosis	0.04	29.6 (1.1-758)

Glucose ≥ 108 mg/dL

Table 6 – Multivariate analysis – Predictors of hyperglycemia* (model adjusted for clinical variables†)

Variables	p	OR (95%CI)
Glucose metabolism	< 0.01	24.1 (4.8-122.1)
Myocardial necrosis	0.03	21.9 (1.3-360.9)
History of diabetes mellitus	0.01	27 (3.7-195.7)

** Glucose ≥ 108 mg/dL. †Clinical variables: age, gender, history of diabetes mellitus, hypertension and dyslipidemia.*

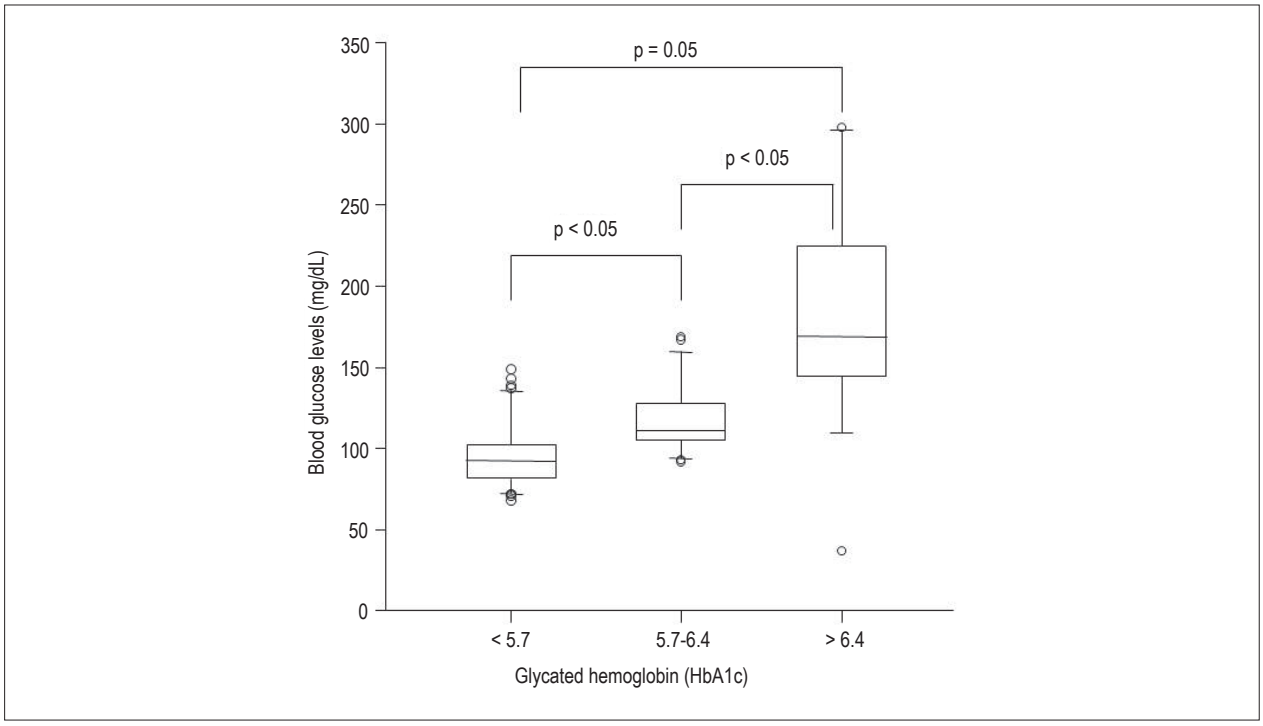

Figure 1 – *Blood glucose levels in patients with acute myocardial infarction according to the glycated hemoglobin (HbA1c) categories: < 5.7% (normal), 5.7-6.4% (glucose intolerance) and > 6.4% (diabetes mellitus).*

and lactic acid was found[36]. The use of magnetic resonance imaging for the determination of the AMI size revealed a significant correlation between the blood glucose levels at admission and AMI extent, regardless of previous changes in glucose metabolism (HbA1c) or necrosis markers[37].

The precise mechanism that explains the impact of hyperglycemia on the AMI extent is not fully understood, but a significant correlation between hyperglycemia and microcirculation abnormalities has already been demonstrated[38]. Clinical studies in patients with AMI undergoing recanalization therapy suggest that hyperglycemia is associated with impaired microvascular function, the so-called no-reflow phenomenon[39]. In addition, there is a clear association between hyperglycemia and heart failure and cardiogenic shock[4,5], that could be explained by a larger AMI size.

Study limitations

The major limitation of the present study is the fact that not all variables which significantly correlate with hyperglycemia in different publications could be analyzed in a single study, such as the present one. However, an extensive literature review was carried out to minimize this limitation, and the authors sought to include the variables with more robust evidence. Another limitation was the inclusion of diabetic patients, which was partially corrected by the construction of a statistical model including history of DM and another pre-specified analysis only for non-diabetic patients.

Conclusion

We concluded that glucose metabolism and myocardial necrosis markers were the best predictors of hyperglycemia in patients with AMI, which suggests a previous undiagnosed impaired glucose metabolism. Thus, these findings corroborate the importance of considering hyperglycemia during the acute phase of AMI as an indicator of glucose intolerance or previous DM.

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Author contributions

Conception and design of the research, Analysis and interpretation of the data: Ladeira RT, Baracioli LM, Faulin TSS, Abdalla DSP, Seydell TM, Maranhão RC, Mendonça BB, Strunz CC, Nicolau JC; Acquisition of data: Ladeira RT, Faulin TSS, Seydell TM; Statistical analysis: Ladeira RT, Castro I, Nicolau JC; Obtaining funding: Ladeira RT, Nicolau JC; Writing of the manuscript: Ladeira RT, Baracioli LM, Mendonça BB, Nicolau JC; Critical revision of the manuscript for intellectual content: Ladeira RT, Baracioli LM, Faulin TSS, Abdalla DSP, Seydell TM, Maranhão RC, Mendonça BB, Strunz CC, Castro I, Nicolau JC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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