Diabetes Mellitus and Glucose as Predictors of Mortality in Primary Coronary Percutaneous Intervention

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Abstract

Background: Diabetes mellitus and admission blood glucose are important risk factors for mortality in ST segment elevation myocardial infarction patients, but their relative and individual role remains on debate.

Objective: To analyze the influence of diabetes mellitus and admission blood glucose on the mortality of ST segment elevation myocardial infarction patients submitted to primary coronary percutaneous intervention.

Methods: Prospective cohort study including every ST segment elevation myocardial infarction patient submitted to primary coronary percutaneous intervention in a tertiary cardiology center from December 2010 to May 2012. We collected clinical, angiographic and laboratory data during hospital stay, and performed a clinical follow-up 30 days after the ST segment elevation myocardial infarction. We adjusted the multivariate analysis of the studied risk factors using the variables from the GRACE score.

Results: Among the 740 patients included, reported diabetes mellitus prevalence was 18%. On the univariate analysis, both diabetes mellitus and admission blood glucose were predictors of death in 30 days. However, after adjusting for potential confounders in the multivariate analysis, the diabetes mellitus relative risk was no longer significant (relative risk: 2.41, 95% confidence interval: 0.76 – 7.59; p-value: 0.13), whereas admission blood glucose remained and independent predictor of death in 30 days (relative risk: 1.05, 95% confidence interval: 1.02 – 1.09; p-value ≤ 0.01).

Conclusion: In ST segment elevation myocardial infarction patients submitted to primary coronary percutaneous intervention, the admission blood glucose was a more accurate and robust independent predictor of death than the previous diagnosis of diabetes. This reinforces the important role of inflammation on the outcomes of this group of patients. (Arq Bras Cardiol. 2014; 103(4):323-329)

Keywords: Diabetes Mellitus; Blood Glucose; Biological Markers; Myocardial Infarction; Percutaneous Coronary Intervention.

Introduction

Diabetes mellitus (DM) is an important risk factor for mortality in patients with ST-segment elevation myocardial infarction (STEMI)[1-3]. In addition, high blood glucose levels on admission are directly related to short-term mortality after STEMI[4-9], regardless of previous diagnosis of DM[10-14] or the reperfusion therapy used[15]. Primary percutaneous coronary intervention (PPCI) is currently the reperfusion therapy of choice in STEMI patients when performed in a timely manner and by experienced cardiologists[16,17]. However, previous studies on the effect of admission glucose levels on clinical outcomes after STEMI are scarce and do not reflect the current practice of interventional cardiology[18-20].

The pathophysiological characteristics of hyperglycemia in STEMI patients are distinct from those observed in DM patients in stable clinical conditions[21]. The most recent guidelines of the European Society of Cardiology reveal some controversies in the acute management of blood glucose levels in STEMI patients and indicate the need for further assessment of this variable during contemporary medical practice[22]. The present study aimed to evaluate the effect of DM and admission hyperglycemia on short-term mortality in STEMI patients subjected to PPCI.

Methods

Experimental design

This unicentric prospective cohort study evaluated all STEMI patients subjected to PPCI at our institution between December 2010 and May 2012. Our hospital is a high-volume tertiary referral center for interventional

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cardiology. It performs approximately 2,500 percutaneous coronary interventions (PCI) per year, and PPCI is the routine reperfusion strategy for STEMI patients. The Research Ethics Committee of this institution reviewed the present study, and all patients enrolled signed a free informed consent form. The authors are solely responsible for the design and conduct of the study, including the analyses, design, manuscript revisions, and approval of the final manuscript. No external funding was provided to support this study.

Patients

STEMI patients hospitalized in our institution and referred to PPCI by the attending physician were included in the study. For most patients, this was their first contact with our institution. STEMI was defined as chest pain at rest for > 30 min, associated with (1) ST-segment elevation of >1 mm in ≥2 contiguous electrocardiographic leads or (2) new left bundle branch block. Exclusion criteria were as follows: chest pain for >12 h, age of <18 years, and patient refusal to enroll in the study.

PPCI was performed as recommended in the literature[17]. Upon admission, all patients were treated with 300 mg of acetylsalicylic acid and 300–600 mg of clopidogrel. Unfractionated heparin (60–100 U/kg) was administered before PPCI. The technical aspects of the procedure, such as type and number of stents, use of adjunct devices, and administration of glycoprotein IIb/IIIa inhibitors, were decided by the cardiologist responsible for PPCI.

Blood samples were collected in the emergency room and analyzed in the hemodynamics room.

Clinical outcomes and patient follow-up

Patients were monitored during hospitalization and by phone contact 1 month after hospital discharge. Coronary flow before and after the procedure was assessed according to the guidelines established by the Thrombolysis in Myocardial Infarction (TIMI) study group[23]. Myocardial perfusion was evaluated using the myocardial blush grade[24]. Stent thrombosis was defined according to the criteria established by the Academic Research Consortium[25]. Delta T was defined as the time between the onset of chest pain and hospital admission. Door-to-balloon time was defined as the time between hospital admission and the first balloon inflation procedure in the artery associated with acute myocardial infarction (AMI). The definition of DM was based on patients' information and use of hypoglycemic therapy.

With regard to follow-up, major adverse cardiac events (MACE) were defined as the combination of death from all causes, new AMI, or stroke. New AMI was defined as recurrent chest pain with an elevation of serum biomarkers, following an initial decline in the natural curve, with ST-segment elevation or new Q waves. Urgent revascularization was defined as both an unplanned revascularization procedure within 30 days after STEMI, and PCI or a coronary artery bypass grafting procedure for the treatment of recurrent ischemia.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 16.0 (SPSS, Inc., Chicago, Illinois). The study power was calculated using the comparison of proportions. Considering the sample size, the power to detect a difference in the 30-day outcome of death between patients with and without DM was 82% using Fisher's exact test. Categorical variables were reported as frequency and percentage. Continuous data were presented as the mean and standard deviation. Variables were considered normal on the basis of the values of central tendency, kurtosis, and skewness in the frequency histograms, in addition to statistical analysis used in previous studies. The chi-square or Fisher's exact test was used for comparisons between categorical variables. The t test was used for comparisons between continuous variables. A p value of <0.05 was considered significant.

Multivariate analysis with stepwise and backward logistic regression models was used to identify independent predictors of cardiovascular mortality 30 days after hospital discharge. Initially, a model including only DM and the GRACE score was adopted to assess the contribution of DM in the rate of events, corrected by a robust score and including comorbidities and clinical variables. Subsequently, a second multivariate analysis was performed, including DM, GRACE score[26,27], and other variables with statistical significance. The dependent variables included in this model were as follows: GRACE score, post-PCI TIMI flow grade 3, DM, delta T, blood glucose, and cholesterol.

Results

During the study period, 740 patients underwent PPCI within the first 12 h after STEMI. DM was present in 134 patients (18%). Table 1 compares the basic characteristics of patients with and without DM. DM patients were older, predominantly women, with a higher frequency of hypertension, dyslipidemia, and previous angina. In DM Patients, smoking was less common, whereas chronic use of aspirin was more frequent. Approximately 40% infarctions occurred on anterior artery walls, with no significant difference between the groups with and without DM. Patients with DM had an increased body mass index and waist circumference compared with those without.

DM patients had higher glucose levels on admission and lower plasma cholesterol levels.

In general, the angiographic profile of patients with and without DM was similar. However, DM patients exhibited a lower Blush 3 score after the procedure (57% vs. 69%; $p < 0.01$). Most of the stents implanted (99.3%) were of the conventional type.

During hospital follow-up, the rates of severe arrhythmia or cardiac arrest (11.5% vs. 7.7%; $p = 0.15$) and stent thrombosis (3.1% vs. 3%; $p = 0.96$) in patients with DM were similar to those in patients without DM. However, the occurrence of acute renal failure (8.5% vs. 2.5%; $p < 0.01$), the need for mechanical ventilation (11.5% vs. 6.5%; $p = 0.04$), and the development of congestive heart failure (13.7% vs. 6.5%; $p = 0.01$) were more frequent

Table 1 – Clinical profile of patients (n = 740) according to the presence or absence of diabetes mellitus

Characteristic	DM (N = 134)	Absence of DM (N = 606)	p value
Age (years)	63 ± 11	60 ± 12	< 0.01
Female (%)	38	29	0.04
Caucasian (%)	90	87	0.43
Hypertension (%)	80	61	< 0.01
Dyslipidemia (%)	47	30	< 0.01
Current smoking (%)	28	45	< 0.01
Family history (%)	26	33	0.13
Medical history			
AMI (%)	27	20	0.06
CABG (%)	5	2	0.19
CRF (%)	3	2	0.63
Angina (%)	48	36	0.01
Daily use of ASA (%)	41	23	< 0.01
ECC, mL/min/1.73 m^2	86 ± 37	87 ± 31	0.81
Total cholesterol (mg/dL)	192 ± 52	204 ± 57	0.02
BMI, (kg/m^2)	27.6 ± 4.3	26.8 ± 4.1	0.05
AC (cm)	96 ± 14	93 ± 15	0.05
SBP (mmHg)	136 ± 32	135 ± 29	0.86
Delta T (hours)	5.2 ± 5.3	4.6 ± 4.3	0.12
DBT (hours)	1.7 ± 1.3	1.56 ± 1.3	0.30
Admission glucose levels (mg/dL)	253 ± 124	143 ± 51	< 0.01

AMI: acute myocardial infarction; CABG: coronary artery bypass grafting procedure; CRF: chronic renal failure; ASA: acetylsalicylic acid; ECC: endogenous creatinine clearance; BMI: body mass index; AC: abdominal circumference; SBP: systolic blood pressure; DBT: door-to-balloon time; DM: diabetes mellitus.

in DM patients. Figure 1 shows a 30-day follow-up as a function of DM. The incidence of MACE (20.1 vs. 11.6; $p < 0.01$) and death (16.4% vs. 7.3%; $p < 0.01$) were higher in patients with DM than in those without.

The multivariate analysis for the 30-day outcome of death was initially performed using DM and GRACE score variables, both of which proved to be predictors of this outcome: GRACE risk score [relative risk (RR): 1.048, 95% confidence interval (CI): 1.037–1.059; $p < 0.01$] and DM (RR: 1.926, 95% CI: 1.016–3.650; $p = 0.04$). The complete model, including other variables and admission glucose levels, is shown in Table 2. We observed that when considering the variables representing the baseline risk of the patient as a result of PPCI and admission glucose levels, DM lost statistical significance. Nevertheless, admission glucose levels were an important predictor of the 30-day outcome of death because an increase of 10 mg/dL in the glucose levels was observed for every 5% increase in RR events (RR: 1.05, 95% CI: 1.02–1.09; $p < 0.01$). The cutoff glucose level for the optimal prediction of the primary outcome was evaluated using the receiver operating characteristic curve, which yielded a glucose level of 159 mg/dL, a sensitivity of 63%, a specificity of 68%, and an area under the curve of 0.65 (95% CI: 0.61–0.69).

Discussion

The present study confirms the increased risk of adverse events for diabetic patients with STEMI subjected to PPCI. Furthermore, it showed that DM is a predictor of short-term events when corrected for the multiple comorbidities represented in the GRACE risk score[26,27]. However, DM lost its statistical significance when other variables, e.g., admission glucose levels, were added to the multivariate model used for predicting 30-day mortality. These results demonstrate the importance of hyperglycemia on admission as a risk factor for short-term events in this context, and suggest that a significant proportion of the risk represented by DM is mediated by admission hyperglycemia, which is more frequent and pronounced in patients with DM compared with those without DM.

Hyperglycemia in DM patients is caused by resistance to insulin and decreased insulin production in pancreatic cells, whereas stress hyperglycemia during AMI and in other serious acute diseases is caused by a complex mechanism of secretion of hormones, including adrenaline, glucagon, growth hormone, and cytokines. In addition to being a marker of the severity of clinical conditions, myocardial damage from stress hyperglycemia may be due to adverse effects

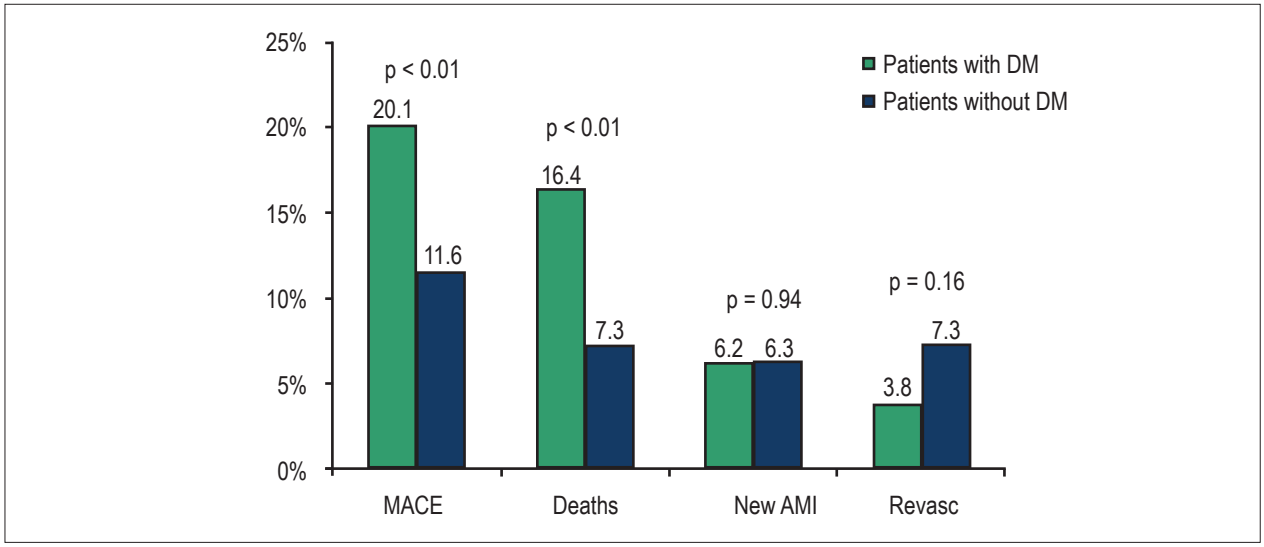

Figure 1 – *Clinical outcomes during a 30-day follow-up (n = 740) as a function of DM. MACE:major adverse cardiac events; new AMI: acute myocardial infarction; Revasc: new revascularization.*

Table 2 – Multiple logistic regression analysis for 30-day mortality

Predictor	Relative risk	95% CI	p value
GRACE score	1.04	1.03 – 1.06	< 0.01
Post-PCI TIMI flow grade 3	0.30	0.12 – 0.71	< 0.01
DM	2.41	0.77 – 7.60	0.13
Delta T	1.08	1.02 – 1.15	< 0.01
Admission blood glucose levels*	1.05	1.02 – 1.09	< 0.01
Total cholesterol	0.99	0.98 – 1.00	0.05

**Admission glucose levels were included in the model in increments of 10 mg/dL.*
PCI: percutaneous coronary intervention; Diabetes mellitus: DM

including increased oxidative stress, platelet activation, and endothelial dysfunction, leading to increased infarct size[21]. Previous studies have shown that hyperglycemia induces an inflammatory response during AMI[28] and that its resolution can restore this response[29]. Two cohort studies of AMI patients (with and without ST-segment elevation) demonstrated that admission hyperglycemia was an independent predictor of in-hospital mortality[30,31] but was not significant for long-term mortality[30]. In addition, admission hyperglycemia had distinct effects on mortality when patients were subdivided into age groups[31]. The analysis of the CARDINAL study indicated that the decreased blood glucose levels in the first 24 h after infarction was associated with decreased 30-day mortality in patients without DM[32].

DM patients have impaired microvascular structure and diffuse endothelial dysfunction, which contributes to decreased blood perfusion, particularly in the context of acute hypoperfusion, such as STEMI[33]. In the present study, the percentage of patients who achieved a Blush 3 score after the procedure was lower in the group with DM, corroborating the results of previous studies[34]. Even with a TIMI flow grade 3 after PPCI, DM patients exhibit less complete resolution of the ST segment after stent implantation, which also indicates impaired microvascular flow[35]. These results corroborate the worse cardiovascular outcomes that DM patients exhibit after STEMI.

Recent studies have suggested that DM is primarily associated with worse long-term outcomes in STEMI patients, whereas the increased cardiovascular risk was primarily due to hyperglycemia. Ishihara et al[18] and Hoebers et al[19] demonstrated that hyperglycemia, but not DM, is associated with short-term adverse events in STEMI patients subjected to PCI. Ergelen et al[20] analyzed the clinical outcome of STEMI patients as a function of DM and blood glucose levels: DM with admission hyperglycemia, DM without admission hyperglycemia, absence of DM with admission hyperglycemia, and absence of DM without admission hyperglycemia. It was observed that patients without DM and with admission hyperglycemia had a higher risk of in-hospital mortality,

whereas DM patients with admission hyperglycemia had the worst long-term outcomes. These results agree with those of Kosiborod et al[7] who, in a large study of AMI patients, showed that the risk of mortality of patients with admission hyperglycemia was higher for those without a DM history, compared with DM patients. This effect is not restricted to STEMI cases because patients admitted to intensive care units with severe acute illnesses and admission hyperglycemia had worse clinical outcomes compared with those having lower glucose levels[36].

Our study reinforces the results reported above and demonstrates that the unfavorable prognostic role of hyperglycemia in short-term adverse events is more relevant and independent than the role of DM[18]. An important advantage of the present study is the inclusion of unselected and consecutive patients, representative of real-world clinical practice. The percentage of DM patients was 18%, which was similar to that reported in other studies (17–21%)[2,34,37].

Limitations

One limitation of the present study involves the lack of data on glycosylated hemoglobin (HbA1c). Approximately 50% of STEMI patients experience changes in glucose metabolism[38], and HbA1c can be a diagnostic criterion of DM[39]. Moreover, it was demonstrated that the prognostic role of admission hyperglycemia is more important than increased HbA1c levels[40], and that HbA1c assumes greater significance in predicting long-term events instead of predicting short-term events[9,11]. The criteria used for the diagnosis of DM (reported by the patient) may have underestimated the number of DM patients. However, it is important to highlight that the percentage of DM patients found herein was similar to that in previous studies, and the blood glucose levels was significantly higher in patients with DM than in those without. Moreover, the assessment of ventricular function during hospitalization was performed by the medical staff, and the study protocol did not include the routine and prospective collection of such data. The large amount of missing data on ventricular function (>25%) prevented the accurate analysis of this variable, and this limitation has occurred in other observational studies on AMI patients subjected to PPCI.

Conclusion

This contemporary analysis with consecutive patients, representative of the clinical practice in a tertiary interventional cardiology hospital, corroborates the increased risk for DM patients subjected to primary angioplasty. It demonstrates the important prognostic role of admission hyperglycemia in predicting short-term adverse cardiovascular events. Furthermore, the latter variable does not depend on other comorbidities or clinical diagnoses, including the diagnosis of DM, and is more important than DM.

Author contributions

Conception and design of the research: David RB, Sebben JC, Gottschall CAM, Quadros AS; Acquisition of data: David RB, Almeida ED, Sebben JC, Feijó IP, Schmidt KES, Avena LM; Analysis and interpretation of the data AND Writing of the manuscript: David RB, Almeida ED, Cruz LV, Quadros AS; Statistical analysis: David RB, Quadros AS; Critical revision of the manuscript for intellectual content: David RB, Almeida ED, Cruz LV, Sebben JC, Feijó IP, Schmidt KES, Avena LM, Gottschall CAM, Quadros AS.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

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