Fasting Glycemia as a Predictor of In-Hospital Mortality in Patients with Acute Myocardial Infarction Undergoing Primary Angioplasty

GERARDO NAU[MTSAC, 1], MARIANO ALBERTAL[2], JORGE THIERER[MTSAC], FERNANDO BOTTO[MTSAC], FERNANDO CURA[MTSAC], LUCIO PADILLA[1], ALFONSINA CANDIELLO[1], SAMIR JOZAMI[1], JORGE BELARDI[MTSAC]

Received: 05/28/2009
Accepted: 07/31/2009

Address for reprints:
Dr. Gerardo Nau
Instituto Cardiovascular
de Buenos Aires
Departamento de Cardiología
Intervencionista y Terapéuticas
Endovasculares
Blanco Encalada 1543 -
Capital Federal
e-mail: g_nau@yahoo.com

SUMMARY

Background
The prognosis of patients with acute ST-segment elevation myocardial infarction (STEMI) has considerably improved, particularly due to reperfusion therapy. However, patients with diabetes mellitus (DM) constitute a high risk group.
In patients with STEMI, hyperglycemia is associated with adverse prognosis, regardless of the previous diagnosis of DM.

Objective
To assess the prognostic value of fasting glycemia (FG) in patients with STEMI undergoing primary angioplasty.

Material and Methods
From a total of 227 patients admitted with STEMI, 31 patients with DM and 7 patients referred to rescue angioplasty were excluded. Glycemia at admission (GAd) and FG were registered; the population was divided according to FG: group A ≥110 mg/dl (hyperglycemic) and group B <110 mg/dl (normoglycemic).

Results
The study population comprised 189 patients. Mean age was 62.1±10.5years, 82% were men and 40% were current smokers; pain-to-balloon time was 2.75 hours (25-75% interquartile range: 2-4.75); 12.1% had a Killip & Kimball (KK) class ≥3, and 38% were anterior wall infarctions. Fifteen patients (7.9%) died during hospitalization; all deaths occurred in hyperglycemic patients. Multivariate analysis identified age (p=0.048) and FG (p=0,002) as independent predictors of mortality; KK class ≥3 (p=0.001), FG (p=0.001), and moderate to severe systolic dysfunction (p=0.016) were independent predictors of major cardiac events (death, reinfarction and heart failure). Glycemia at admission was not identified as an independent predictor of death or major cardiac events.

Conclusions
The results of the present study suggest that FG has a prognostic value in the short term in non diabetic patients with STEMI. Fasting glycemia is a simple tool for the early identification of a high risk population.

Rev Argent Cardiol 2009;77:361-366.

Key words > Myocardial Infarction – Glycemia – Primary Angioplasty

Abbreviations >

CK	Creatine Kinase	**STEMI**	ST-segment elevation acute myocardial infarction
CK-MB	Creatine Kinase MB fraction	**CHF**	Congestive heart failure
DM	Diabetes mellitus	**KK**	Killip & Kimball
FG	Fasting glycemia	**ReMI**	Reinfarction
AG	Admission glycemia	**IQR**	Interquartile range
AMI	Acute myocardial infarction		

[MTSAC] Full Member of the Argentine Society of Cardiology
Instituto Cardiovascular de Buenos Aires
[1] Department of Interventional Cardiology and Endovascular Therapy
[2] Research Department

BACKGROUND

The prognosis of patients with acute ST-segment elevation myocardial infarction (STEMI) has considerably improved, particularly due to reperfusion therapy. (1, 2) Despite this progress, patients with diabetes mellitus (DM) constitute a high risk group. (3) In epidemiologic studies the incidence of microvascular and macrovascular complications was greater with considerably lower blood glucose levels than those defined for the diagnosis of DM ("impaired glucose tolerance".) (4, 5)

Among nondiabetic patients admitted due to STEMI with hyperglycemia, 40% have impaired glucose tolerance and 25% are have newly diagnosed DM. (6)

Admission hyperglycemia is associated with increased short-term morbidity and mortality and with worse outcomes in the long-term follow-up of nondiabetic patients. (7-9) This worse outcome might be due to more severe systemic atherosclerotic compromise and hemodynamic impairment secondary to less myocardial reperfusion and functional recovery. (7, 9, 10) However, admission glycemia (AG) is an unspecific marker as it is subjected to multiple variables.

During a stressful situation, adrenergic activation and incipient failure of pancreatic beta-cells increase blood glucose levels. Metabolic abnormalities, such as increased fatty acids and hyperglycemia increase the severity of ischemic damage. (11)

The goal of our study was to investigate the association between fasting glycemia (FG) and mortality in nondiabetic patients with STEMI undergoing primary angioplasty.

MATERIAL AND METHODS

The study was performed between January 1998 and December 2005. All patients with a diagnosis of STEMI within 24 hours from symptoms onset were consecutively and prospectively included into a database of the Department of Interventional Cardiology and Endovascular Therapy of the *Instituto Cardiovascular de Buenos Aires*. STEMI was defined following the TIMI criteria: ischemic discomfort at rest lasting > 20 minutes associated with new ST-elevation > 1 mV in 2 or more contiguous ECG leads and total CK > 2x , CK-MB elevation upper limit of normal or rise of troponin with at least one value above the 99th percentile of the upper reference limit. The diagnosis of reinfarction (reMI) and congestive heart failure (CHF) was also defined according to the TIMI study group. All patients underwent a primary percutaneous coronary intervention. Complete reperfusion was considered in the presence of the sum of ST-segment elevation resolution ≥ 70% 60 minutes after revascularization when the patient was admitted to the coronary care unit.

Patients already diabetics and those with AMI related to the procedure, reMI or a history of surgery within the previous month were excluded from the analysis. For the diagnosis of DM the patient was required to be aware of his/her diabetic condition, to be following a diabetic diet or to receive treatment with oral hypoglycemic agents and/or insulin. (4, 10)

The determinations of blood glucose levels were obtained within the first 24 hours after hospitalization. Admission glycemia and FG (between 8 and 12 hours after admission) were determined by the glucose oxidase method.

Correction dose of regular insulin were not used during this period. All patients underwent transthoracic echocardiography before discharge to determine ventricular function, ventricular volumes and wall motion.

Blood glucose levels of patients without a previous diagnosis of diabetes were classified according to the guidelines of the American Association of Diabetes. Fasting hyperglycemia was defined as blood glucose levels ≥ 110 mg/dl. (4)

The population was divided into two groups according to FG values: group A ≥ 110 mg/dl (hyperglycemic patients) and group B < 110 mg/dl (normoglycemic patients).

Patients' baseline characteristics were compared between groups, as well as angiographic findings, therapies, procedure-related issues, mortality rate and major adverse cardiac events (death, reIM, CHF) during hospitalization.

Clinical follow-up included medical visits and/or telephone contact during 6 months after discharge with the aim of identifying patients with a new diagnosis of DM.

Statistical Analysis

Categorical variables were expressed as percentages and continuous variables as means and standard deviation or medians with their corresponding 25-75% interquartile range (IQR). Student's *t* test and chi square test were used to compare the variables between both groups. The association between baseline variables with events was expressed as odds ratio (OR) and its corresponding 95% interval confidence (CI). Simple logistic regression analysis was used to evaluate the different variables: age, gender, previous MI, number of leads with ST-segment elevation, complete resolution of ST-segment elevation, chronic kidney failure, peripheral vascular disease, CK levels, creatinine levels, white blood cell count, baseline heart rate and systolic blood pressure, Killip class, left ventricular function during hospitalization, AG and FG. All those variables with a p value < 0.10 in the simple logistic regression were included in the multivariate analysis to identify independent predictors of morbidity and mortality. A p value < 0.05 was considered statistically significant.

RESULTS

From a total of 227 patients admitted with STEMI, 31 patients with DM and 7 patients referred to rescue angioplasty were excluded. A total of 189 patients were finally included in the analysis with complete clinical data and laboratory tests. Table 1 summarizes baseline demographic characteristics of the general population and stratified by fasting glycemia. Twenty one percent of patients had previous myocardial infarction, 12.1% had been admitted with hemodynamic compromise (KK ≥ 3); median AG and FG were 132 mg/dl (IQR 113-165) and 109 mg/dl (IQR 95-134), respectively. The characteristics of the procedure are described in Table 2. The compromise of the infarct-related artery has a typical distribution in this population. Complete reperfusion occurred in 60% of patients, and the proportion of final TIMI grade 3 flow was 82.4% (see Table 2).

Comparison between pre- and post-procedure variables in both groups

Patients with hyperglycemia (n = 94, 49.7%) were older (p < 0.001) and had worse Killip class compared to patients with normoglycemia (p < 0.004; see Table

Table 1. Demographics

	Total population (n = 189)	Hyperglycemic patients (n = 94)	Normoglycemic patients (n = 95)	p
Age (years)	62.1 ± 10.5	64.6 ± 9.5	59,5 ± 11	< 0,001
IMC	25.5 ± 13.4	26.6 ± 12.4	25.1 ± 13.1	0.03
HT	109 (57.6%)	55 (58.5%)	54 (56.8%)	0.81
Dyslipemia	106 (56.1%)	51 (54.3%)	55 (57.9%)	0.61
Current smoking	77 (40.7%)	37 (39.3%)	40 (42.1%)	0.70
IQR	6 (3.1%)	4 (4.2%)	2 (2.1%)	0.40
Previous AMI	41 (21.7%)	23 (24.5%)	18 (18.9%)	0.36
Previous PCI	17 (8.9%)	7 (7.5%)	10 (10.5%)	0.46
Previous CABGS	5 (2.6%)	2 (2.1%)	3 (3.1%)	0.89
Baseline SBP (mm Hg)	123 ± 23.3	123.7± 25.4	122.9 ±21.1	0.80
HR (bpm)	73 ± 19.3	75.7 ± 22.8	70.4 ± 14.8	0.06
Time of ischemia (hs)	2.75 (2-4.5)	3 (2-5)	2.5 (2-4)	0.20
KK ≥ 3	23 (12.1%)	18 (19.2%)	5 (5.3%)	0.004
Peak CK (IU)	1.539 (777-2.553)	1.895(990-3.218)	1.300 (643-1.994)	< 0,001
Creatinine level (mg/dl)	1.16 ± 0.35	1.22 ± 0.39	1.10 ± 0.29	0.01
White blood cell count	12.325 ± 4.620	12.936 ± 4.534	11.600 ±4.100	0.001
AG (mg/dl)	132 ± 72.7	171.8± 76.4	129.09 ± 73.5	< 0.001
FG (mg/dl)	109 ± 50.2	151.8± 54.1	95.6 ± 49.2	

Categorical variables are expressed in n (%) and continuous variables as means and standard deviation or medians with IQR. BMI: Body mass index. HT: Hypertension. LAD: Left anterior descending. CKF: Chronic kidney failure. PCI: percutaneous coronary intervention. CABGS: Coronary artery bypass graft surgery. SBP: Systolic blood pressure. HR: Heart rate. CK: Creatine Kinase. FG: Fasting glycemia. AG: Admission glycemia.

1). Fasting glycemia > 110 mg/dl was associated with a greater peak value of cardiac enzymes ($p < 0.001$) and worse left ventricular function ($p = 0.036$; see Table 2). By the end of the procedure this group had a lower rate of complete reperfusion ($p < 0.01$) and TIMI grade 3 flow compared to group B ($p = 0.03$; see Table 2).

Comparison of clinical outcomes during hospitalization between groups

Fifteen patients (7.9%) died during hospitalization; all deaths occurred in hyperglycemic patients. In addition, AG was significantly greater among the decedents compared to those who survived (230 versus 130 mg/dl; OR 1.01, 95% CI 1.008-1.024; $p < 0.01$).

Patients with hyperglycemia had a greater incidence of major cardiac events, CHF ($p < 0.001$) and reMI ($p < 0.001$) compared to group B (see Table 2).

Predictors of in-hospital mortality and morbidity

Two models of logistic regression analysis were constructed to predict in-hospital mortality considering the different clinical and hemodynamic variables and the results of the lab tests. The area under the ROC curve was 0.92 in a first multivariate model that included only AG. A second logistic regression included only FG as a continuous variable, as all the decedents belonged to the group with FG ≥ 110 mg/dl. In this case, the area under the ROC curve was 0.97. When FG and AG were simultaneously incorporated to multivariate analysis, the latter variable did not prove to be an independent predictor of mortality. Multivariate analysis identified age ($p = 0.048$) and FG ($p = 0.002$) as independent predictors of in-hospital mortality (Table 3).

In addition, increased FG ($p = 0.001$), KK ≥ 3 at admission ($p = 0.001$), and moderate to severe left ventricular dysfunction ($p = 0.016$) during hospitalization were identified as independent predictors of major adverse cardiac events (Table 4).

DISCUSSION

Several studies have been published on the prognostic evaluation of glycemia in acute coronary syndrome. Yet, there is a great heterogeneity of populations and definitions. Firstly, there is no definition of hyperglycemia in patients under acute conditions. This is reflected by the marked difference of patients with stress hyperglycemia in different studies (from 3% to 71%). [(8) The percentage of fasting hyperglycemia in this study was 50% using a cut-off point of 110 mg/dl. This percentage seems to be high and has marked a significant difference between both populations. Continuing with the problem of the lack of definitions, most of the published studies have used blood glucose

	Total population (n = 189)	Hyperglycemic patients (n = 94)	Normoglycemic patients (n = 95)	p
LAD infarct-related artery	72 (38.1%)	40 (42.5%)	32 (33.7%)	0.21
Complete reperfusion	111 (58.7%)	41 (43.7%)	70 (73.7%)	< 0.001
Previous TIMI grade flow 0	147 (77.7%)	71 (75.5%)	76 (80%)	0.93
Final TIMI grade flow 3	156 (82.4%)	64 (68%)	92 (96.8%)	0.023
M/S LVD	101 (43.4%)	63 (67%)	38 (40%)	0.036
reMI	9 (4.7%)	6 (6.4%)	3 (3.2%)	0.30
CHF	33 (17.4%)	27 (28.7%)	6 (6.3%)	< 0.001
CS	22 (11.6%)	21 (22.3%)	1 (1%)	< 0.001
Death	15 (7.9%)	15 (16%)	0 (0%)	< 0.001
Death/CHF/reMI	28 (14.8%)	24 (25.5%)	4 (4.2%)	< 0.001

CHF: Congestive heart failure. ReMI: Reinfarction. CS: Cardiogenic shock. M/S LVD: Moderate/severe left ventricular dysfunction.

Table 2. Characteristics of the procedure and clinical outcomes

	Odds ratio	SE	p	95% CI
Age	1.15	0.08	0.048	1.001-1.320
BMI	0.74	0.13	0.09	0.58-1.04
HR (bpm)	1.003	0.02	0.88	0.96-1.04
Baseline SBP (mm Hg)	0.98	0.02	0.41	0.94-1.03
Creatinine level	3.51	5.93	0.46	0.13-9.19
White blood cell count	1.000	0.01	0.34	0.999-1.000
AG	1.001	0.01	0.88	0.99-1.016
FG	1.05	0.02	0.002	1.02-1.08
KK 3-4	0.32	0.38	0.33	0.003-3.26
M/S LVD	0.94	1.02	0.95	0.11 – 7.88
Final TIMI grade flow 3	0.62	0.64	0.65	0.08 – 4.70

SE: Standard error. CI: Confidence interval. BMI: Body mass index. HR: Heart rate. SBP: Systolic blood pressure. AG: Admission glycemia. FG: Fasting glycemia. KK: Killip & Kimball. M/S LVD: Moderate/severe left ventricular dysfunction.

Table 3. Mortality prediction model

	Odds ratio	SE	p	95% CI
Age	1.07	0.04	0.06	0.99-1.14
HR (bpm)	0.99	0.02	0.761	0.96-1.03
Baseline SBP (mm Hg)	1.008	0.02	0.635	0.97-1.04
Creatinine level (mg/dl)	3.54	2.77	0.107	0.76-16.42
FG	1.03	0.009	0.001	3.46-46.92
KK ≥ 3	12.73	8.47	0.001	5.76-539.44
M/S LVD	8.47	7.51	0.02	1.49-48.16
Final TIMI grade flow 3	0.62	0.00	0.53	0.14-2.75
Peak CK	0.999	0.0002	0.07	0.998-1.000
Previous AMI	0.91	0.71	0.90	0.19-4.19

SE: Standard error. CI: Confidence interval. HR: Heart rate. SBP: Systolic blood pressure. FG: Fasting glycemia. KK: Killip & Kimball. M/S LVD: Moderate/severe left ventricular dysfunction. CK: Creatine Kinase. AMI: Acute myocardial infarction.

Table 4. Major adverse cardiac events prediction model

values obtained during admission. (15-18) Ravid et al. (19) and Soler and Frank (20) demonstrated greater mortality using a cut-off point of 144 mg/dl of AG. Yet, the greater number of patients with newly diagnosed DM, the type of treatments used and the low incidence of reperfusion deserve to be mentioned.

Zeller et al (21) studied the prognostic value of FG with a cut-off point between 110 mg/dl and 126 mg/dl and demonstrated that glycemia predicted cardiogenic shock but not mortality. Sulleiman et al (12) compared AG and FG in 735 nondiabetic patients with STEMI undergoing different therapeutic strategies (thrombolysis, primary PCI, and medical treatment). Patients were divided into tertiles. Mortality at 30 days was significantly greater in patients with elevated FG and AG. In our study, we excluded patients treated with thrombolysis and those with AMI lasting longer than 24 hours. We only analyzed patients undergoing PCI with a relatively short pain-to-balloon time. These characteristics and the use of FG make this population more homogeneous and less variable. Therefore, FG is a stronger and less dependent variable that determines a 5% increase in the risk of death for each 1mg/dl increase. Several hypotheses try to explain the correlation between stress hyperglycemia and adverse events. From a physiopathological point of view, elevated catecholamines and cortisol produce insulin resistance that reduces myocardial glucose uptake. This promotes increased circulating free fatty acids which have direct toxicity and reduce glucose uptake and oxidation. (22) Hyperglycemia produces endothelial dysfunction, greater oxidative stress and hypercoagulability. (23) A recent study has demonstrated an association between elevated glucose levels and rethrombosis of the infarct-related artery after thrombolytic therapy. (24) In the present experience, hyperglycemic patients undergoing percutaneous revascularization presented lower final TIMI grade flow and electrocardiographic signs of reperfusion that were neither related to the impaired cardiac territory nor to the duration of ischemia.

After 6 months of follow-up, 5% of these patients presented newly diagnosed DM and 15% developed impaired glucose tolerance. The low percentage of patients who subsequently developed DM identifies a little contaminated population, as previous studies showed a greater percentage of diabetics who were unaware of their condition before the event. (25)

CONCLUSIONS

Hyperglycemia in STEMI patients undergoing primary PCI proved to be a simple and independent early marker of in-hospital mortality. A prognostic definition of hyperglycemia is needed in this population for better risk stratification and evaluation of the benefit of early treatment of acute hyperglycemia, in order to achieve better in-hospital outcomes and to promote a standardized control of metabolic abnormalities.

BIBLIOGRAPHY

1. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986;1:397-402.

2. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413-9.

3. Malberg K, Rydén L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988;9:259-64.

4. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.

5. Balkau B, Shipley M, Jarrett RJ, Pyörälä K, Pyörälä M, Forhan A, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998;21:360-7.

6. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 2002;359:2140-4.

7. Iwakura K, Ito H, Ikushima M, Kawano S, Okamura A, Asano K, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol 2003;41:1-7.

8. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773-8.

9. Cao JJ, Hudson M, Jankowski M, Whitehouse F, Weaver WD. Relation of chronic and acute glycemic control on mortality in acute myocardial infarction with diabetes mellitus. Am J Cardiol 2005;96:183-6.

10. Marfella R, Siniscalchi M, Esposito K, Sellitto A, De Fanis U, Romano C, et al. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. Diabetes Care 2003;26:3160-7.

11. Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 1994;343:155-8.

12. O'Sullivan JJ, Conroy RM, Robinson K, Hickey N, Mulcahy R. In-hospital prognosis of patients with fasting hyperglycemia after first myocardial infarction. Diabetes Care 1991;14:758-60.

13. Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, et al. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. Circulation 2005;111:754-60.

14. Stranders I, Diamant M, van Gelder RE, Spruijt HJ, Twisk JW, Heine RJ, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. Arch Intern Med 2004;164:982-88.

15. Timmer JR, van der Horst IC, Ottervanger JP, Henriques JP, Hoorntje JC, de Boer MJ, et al; Zwolle Myocardial Infarction Study Group. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. Am Heart J 2004;148:399-404.

16. Oswald GA, Smith CC, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. Br Med J 1986;293:917-22.

17. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 2002;359:2140-4.

18. Bolk J, van der Ploeg T, Cornel JH, Arnold AE, Sepers J, Umans VA. Impaired glucose metabolism predicts mortality after a myocardial infarction. Int J Cardiol 2001;79:207-14.

19. Ravid M, Berkowicz M, Sohar E. Hyperglycemia during acute myocardial infarction. A six-year year follow-up study. JAMA 1975;233:807-9.

20. Soler NG, Frank S. Value of glycosilated hemoglobin measurements after acute myocardial infarction. JAMA 1981;246:1690-3.
21. Brindisi MC, Dentan G, Laurent Y, Janin-Manificat L, et al. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. Eur Heart J 2004;25:308-12.
22. Lopaschuk GD, Stanley WC. Glucose metabolism in the ischemic heart. Circulation 1997;95:313-5.
23. Taegtmeyer H, Mc Nulty P, Young ME. Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation 2002;105:1727-33.
24. Pinto DS, Kirtane AJ, Pride YB, Murphy SA, Sabatine MS, Cannon CP, et al; CLARITY-TIMI 28 Investigators. Association of blood glucose with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction (from the CLARITY-TIMI-28 study). Am J Cardiol 2008;101:303-7.
25. Tenerz A, Lönnberg I, Berne C, Nilsson G, Leppert J. Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? Eur Heart J 2001;22:1102-10.