Insulin Resistance and Short-Term Mortality in Patients with Acute Myocardial Infarction

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Abstract

Background: Homeostasis Model Assessment (HOMA) is a widely used index to study the role of insulin resistance (IR).Our objective has been to clarify if IR would predict short-term mortality in patients with acute myocardial infarction (AMI).

Methods: Observational prospective study in 518 consecutive patients with a clinical diagnosis of AMI with or without diabetes mellitus. We evaluated glucose and insulin levels at baseline in order to estimate IR and mortality. Association between IR and mortality was assessed by means of the Cox regression analysis, and discriminative accuracy of the multivariate model with the Harrell's C statistic.

Results: In-hospital mortality was 6% (32/518 of patients). Using ROC curve, in non-diabetic patients, IR index >2.2 was the best cut-off for predicting in-hospital mortality with a sensitivity of 71% and specificity of 80% (AUC=0,710) (p=0,008). An IR>2.2 was present in 27% (140 patients) and this group had higher rates of NYHA>2, Body Mass Index ≥30, hypertension and diabetes mellitus. Harrell's C statistic of 0.967 was obtained when an IR>2.2 was used in the model to predict mortality. Furthermore, mortality rose as IR values increased, from 3% IR<2 to 18% when IR>3.5. In multivariate adjusted hazard ratio analysis IR>2.2 was an independent factor for in-hospital mortality (HR=3.4; 1.2-9) (p=0.017) in addition to age >70 years (HR=3.2; 1.04-10) (p=0.04) and Killip class >1 (HR=4; 1.4-14) (p=0.012).

Conclusions: Beyond traditional cardiovascular risk factors, insulin resistance as assessed by HOMA index, seems to strongly influence prognosis and could be included in the routine clinical work up of patients with acute myocardial infarction.

Keywords: Acute myocardial infarction; Diabetes mellitus; Insulin resistance; HOMA

Abbreviations: HOMA: Homeostatic Method Assessment; IR: Insulin Resistance; AMI: Acute Myocardial Infarction; ROC: Receiver Operating Characteristic; AUC: Area Under Curve; NYHA: New York Heart Association; HR: Hazard Ratio; STEMI: ST Elevation Myocardial Infarction; NSTEMI: Non ST Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; BMI: Body Mass Index; DM: Diabetes Mellitus; CRP: C-reactive protein; CPK: Creatinine Phosphokinase; CK-MB: Creatinine Kinase Muscle Brain Isoenzyme; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; ECLIA: Electrochemiluminescence Immunoassay; OR: Odds Ratio

Introduction

In the early phase of Acute Myocardial Infarction (AMI) with or without previously known diabetes, the acute glucose metabolism is quite complex, comprising increased glucose values and the development of acute insulin resistance (IR). It is not clear whether the elevated glucose level in the early, unstable phase of the AMI reflects abnormal glucose metabolism (stable disturbances of glucose regulation preceding the AMI) or is a marker of stress and/or severity of myocardial damage [1-4]. Moreover it has been recently observed that a higher glucose reading on admission has shown a higher prevalence of life-threatening arrhythmia and mortality, mainly in non-diabetic patients with AMI [5].

Insulin resistance (IR) is typically defined as a decreased sensitivity or responsiveness to metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production. IR plays a major pathophysiological role in type 2 diabetes and is tightly associated with major public health problems, including obesity, hypertension, coronary artery disease, dyslipidemias and a cluster of metabolic and cardiovascular abnormalities that define the metabolic syndrome [6]. Homeostatic Model Assessment (HOMA) developed by Matthews et al in 1985, [7] is a useful model for evaluation of IR in individuals with glucose intolerance, mild to moderate diabetes, and other insulin-resistant conditions. Both the original and the updated HOMA2, assume a feedback loop between the liver and pancreatic β-cell [8,9].

Few studies assessed the role of IR, evaluated by means of HOMA index in the early phase of AMI in patients with and without previously known diabetes [10,11]. In this patients with elevated HOMA have been observed a higher incidence of previous cardio and cerebrovascular events [12]. Moreover, several studies have suggested that although IR is associated with traditional risk factors, it may influence independently the progression of coronary atherosclerotic plaques in asymptomatic patients, also in virtue of the correlation with endothelial dysfunction [13,14].

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The well-known relationship among impaired glucose metabolism, insulin resistance, cardiovascular disease and the novel finding of an unexpected prevalence of abnormal glucose metabolism in unselected patients with AMI group strengthened our interest in further exploring the metabolic profile of these patients. The aim of our study was to evaluate the role of IR by means of the HOMA index in the early phase of acute myocardial infarction.

Materials and Methods

This was a single-centre observational prospective study. We studied 518 subjects, 361 (75%) males, all referred to our Coronary Care Unit for AMI, from January 2009 to July 2011. The entry criteria for the study were: chest pain with ST segment elevation (STEMI) or depression (NSTEMI) of at least 1 mm in one or more peripheral leads of the ECG and/or at least 2 mm in one or more precordial leads or acute bundle branch block according to the criteria established by current guidelines [15]. Subjects were excluded from the study if they had acute inflammatory diseases, hepatic failure, autoimmunity or cancer.

The project design included a medical examination, biochemical analyses and instrumental exams as echocardiography and coronary angiography results. All patients with no specific contraindications received the recommended drugs in the acute phase. Patients with STEMI and having contraindication for thrombolytic therapy were referred for urgent invasive angiography with the intention of performing Primary Percutaneous Coronary Intervention (PCI). Moreover, patients after unsuccessful fibrinolytic therapy were treated with rescue PCI. Echocardiography was included in this study, in order to discern left ventricular function. We also evaluated the number of coronary vessels when angiography was performed.

All diabetic and non-diabetic patients with hyperglycaemia in the acute phase of AMI were treated with subcutaneous short-acting insulin according to digital glycemia test. After discharge from the Coronary Care Unit, elevated glycemia was treated with long-acting insulin twice daily. Patients who required a continuous infusion of insulin were excluded from study.

Among the main cardiovascular risk factors, the presence of hypertension, type II diabetes, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, smoking habits and body mass index (BMI) were considered. Hypertension was defined as being a history of regular antihypertensive drug therapy or a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥85 mmHg. Obesity: subjects with a Body Mass Index ≥30 were classified as being obese. Smoking: subjects who smoked when included into the study or had stopped smoking within the last 1 year were classified as smokers. Diabetes Mellitus (DM) group included patients with a prior history of diabetes obtained from hospital records and those reporting a diagnosis of DM or receiving pharmacologic treatment (oral hypoglycaemic drugs or insulin) or diet control. Patients with a fasting glucose level <110 mg/dl and without a history of diabetes were classified as normoglycemic [16]. Urine specimens collected in the morning after admissions were analyzed for albumin and creatine; results were considered positive if the albumin-to-creatinine ratio was ≥20 mg/g [17].

Assessment of the metabolic status and insulin resistance by homeostatic model assessment

All analyses were measured by conventional laboratory methods. In the emergency department the following analyses were collected: serum glucose, haemoglobin, C-reactive protein (CRP), white blood cell count, platelets, haematocrit, electrolytes, creatinine phosphokinase (CPK), creatinine kinase muscle brain isoenzyme (CK-MB). In addition, blood samples were also collected within 24 hours of admission for total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol.

Plasma insulin and C-peptide concentration were analyzed in fasting samples taken on the first morning after admission. Plasma insulin was quantified using the second generation electrochemiluminescence immunoassay (ECLIA) sandwich principle, with two mouse monoclonal insulin-specific antibodies Elecsys analyzer (Roche Diagnostics, Mannheim, Germany). HOMA2-IR online calculator downloaded from http://www.dtu.ox.ac.uk was used to calculate IR in fasting conditions.

Because stress HOMA cut-off values are poorly defined in patients with AMI, our proposed HOMA threshold was based on optimizing the sum of sensitivity and specificity, derived from receiver operating characteristic (ROC) curves, which predict the development of in-hospital mortality [18-21].

Follow-up was closed on July 1st 2011. The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

Statistical analysis

Continuous variables with abnormal distribution (Kolmogorov–Smirnov test) were transformed by neperian logarithm before analysis. Continuous variables were expressed as mean ± standard deviation or standard error mean, determining the differences between groups by Student's t-test. The categorical variables were compared by chi-square analysis. The relationship between continuous variables was examined using the Pearson or Spearman correlation co-efficient. ROC curve analysis was used to assess the ability of various levels of HOMA2-IR to predict mortality. The significant variables in the univariate analysis were introduced in a multivariate logistical regression model to obtain the predictive variables of adverse outcomes (in-hospital mortality). The proportionality assumption for the hazard function over time was tested by means of Schoenfeld residuals. The model's discriminative ability was assessed with the Harrell's C statistic and its calibration by the Gronnesby and Borgantest. Event rate for in-hospital mortality was determined using the Kaplan–Meier method and compared using the log-rank test. A p-value of <0.05 was considered statistically significant for all analyses. Data were analyzed using the Statistical Package for Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Median time from onset of chest pain to hospital admission was 3 h (range 1–48 h). The median age of our sample was 65 (30-95) years, 75% were males and BMI>30 was present in 24% of patients. STEMI was observed in 63% (329/518 of patients) and thrombolytic therapy was administrated in 35% (115/329 of STEMI patients) of patients. A PCI was performed in 88% (456/518 of patients) and primary percutaneous coronary angioplasty was carried out in 28% of patients with STEMI. Patients were discharged from hospital after a median of 8 days (range 1–36 days).

HOMA2-lR, clinical, hemodynamic and metabolic parameters

Using ROC curve, in non-diabetic patients, IR index >2.2 was the

best cut-off for predicting in-hospital mortality with a sensitivity of 71% and specificity of 80% (AUC=0.710, CI=0.53-0.89) (p=0.008). DM as a cardiovascular risk factor was present in 180/518 (34%) patients and in these patients, mortality in unadjusted analysis, was higher than in patients without DM (10% vs 4%) (p=0.008), OR= 1.7 (1.2-2.3). Furthermore, we did not find IR cut-off value for predicting in-hospital mortality in patients with known DM (AUC= 0.51 (0.40-0.72) (p=0.42).

Non-parametric correlation (Spearman's) showed that HOMA index was significantly positive correlated with anthropometric measurement (BMI) (r= 0.250; p<0.001) and some biochemical and metabolic variable (proteinuria r=0.142; p=0.006), fasting glycemia (r=0.451, p<0.001), triglyceride (r=0.167, p=0.001).

Clinical, hemodynamic and metabolic characteristics of the study population according to HOMA2-IR are presented in Table 1. Subjects were divided into two groups according to HOMA index value: 1º) Patients at elevated HOMA>2.2 and 2º) Patients at low HOMA≤2.2 which represents the control group. Insulin Resistance (IR>2.2) was detectable in 27% of patients and was associated with previous cardiovascular diseases, hypertension, DM and chronic myocardial infarction.

Hospital outcome

Patients with IR>2.2 required more inotropic agents (OR=3) (digital, dopamine, dobutamine, levosimendan) and diuretic drugs (OR=1.6) than patients with IR≤2.2, during in-hospital stay. Focusing our attention to mortality, in-hospital mortality was 6% (32/518 of patients). The incidence of mortality grows contemporary to the increasing of HOMA (Figure 1): IR<2 had an in-hospital mortality

| Variable	HOMA2-IR >2.2 (140 patients)	HOMA2-IR ≤2 (378 patients)	OR (CI)	P
Anthropometric Parameters				
Male	74%	77%	0.8 (0.6-1.2)	0.4
Aged (m ± sd)	66±12	64±13		0,13
BMI (kg/m²)	29±4	27±4		0,001
BMI > 30 (kg/m²)	32%	21%	1.5 (1-2)	0.03
Previous Disorders				
NYHA>2	11%	3%	2.4 (1.6-3.5)	0.001
Diabetes	48%	29%	1.8 (1.3-2.4)	0.001
Hypertension	73%	60%	1.5 (1.1-2.2)	0.012
Previous Myocardial Infarction	31%	21%	1.4 (1-1.9)	0.05
Current smoker	32%	42%	0.7 (0.5-1)	0.045
Dyslipemia	54%	52%	1 (0.78-1.4)	0.66
Chronic Renal Disease	19%	6%	1.5 (0.9-2.4)	0.12
Metabolic Syndrome	71%	39%	2.7 (2-3.7)	<0.001
Acute Myocardial Infarction				
Killip>1 (admission)	43%	24%	0.8 (0.6-1.1)	<0.001
Left Ventricular EF (243 patients)	48±15	53±11	1.8 (1.3-2.5)	0.020
Percutaneous Coronary Intervention	88.3%	88%	1 (0.66-1.5)	0.99
Coronary Artery Affected>1	50%	31%	2.8 (2.1-3.7)	0.001
Coronary Artery Disease	1.9±1	1.4±0.8		<0.001
CK-MB (m ± st. error mean)	138±15	132±8		0.7
In-Hospital Mortality	15.5%	2.5%	2.8 (2-3.8)	<0.001
In-Hospital Stay (m ± sd)	11.8±9	9.8±6		0.023
Metabolic and Inflammatory parameters				
Glycemia (mg/dL) (admission)	193±87	156±68		<0.001
Fasting Glycemia (mg/dL)	160±64	115±37		<0.001
HbA1c (%)	6.7±1.4	6±1.2		<0.001
Insulin (µU/ml)	29±24	8±8		<0.001
C-peptide (ng/ml)	5.4±4	3±1.3		<0.001
Triglyceride (mg/dL)	166±88	135±84		<0.001
Triglyceride > 150 mg/dL	42%	28%	1.56 (1.15-2)	0.004
Cholesterol (mg/dL)	180±52	177±46		0.6
HDL (mg/dL)	42±15	43±11		0.3
LDL (mg/dL)	112±51	111±40		0.8
Creatine (mg/dl)(admission)	1.38±1.2	1.1±0.7		0.04
Albuminuria/creatinuria*	96±16	62±8		0.001
Albuminuria >20 mg/dL	67%	42%		<0.001
CRP (admission)(mg/L)*	29±4	25±2	2.2 (1.5-3)	0.4
WBC (admission)(10⁹/L)	11,176±3,702	11,355±8,54		0.5
Pharmacologic Treatment				
Aspirin	96%	96%	1 (0.47-2.2)	0.94
Clopidogrel	84%	88%	0.78 (0.5-1.1)	0.26
Heparin	85%	80%	1.3 (0.8-2)	0.23
B-Blockers	32%	31%	1 (0.4-1.2)	0.6
ACE inhibitors	60%	61%	0.89 (0.6-1.2)	0.46
Statin	87%	91%	0.7(0.48-1.1)	0.21
Diuretics	43%	26%	1.7 (1.2-2.3)	0.001
Inotropic agents	17%	6%	2 (1.4-2.9)	0.001
Insulin (163 patients) (35%)	52%	29%	1.9 (1.4-2.6)	0.001

NYHA: New York Heart Association. STEMI: ST elevation myocardial infarction. CK-MB: Creatine Kinase MB. HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein. PCI: Percutaneous Coronary Intervention. CRP: C-Reactive Protein. WBC: White Blood Cell

Table 1: Acute myocardial infarction: Clinical, hemodynamic and metabolic characteristics of the study population according to HOMA2-IR.

of 3% (10/340) meanwhile higher mortality was observed in patients with IR>3.5 (18%) (11/60). Patients with IR 2-3.5 had an intermediate mortality (9%) (11/118).Moreover, patients with IR>2.2 exhibited 2.7-fold increase of mortality than those with IR≤2.2 in unadjusted analysis (Table 1). Figure 2 shows cumulative survival (Kaplan–Meier) in patients with acute myocardial infarction according to the HOMA2-IR cut-off; difference between the curves was statistically significant with the log rank test=21 (p <0.001). In Figure 3 we can observe logistic regression model in the stratification of all patients with AMI. Adjusted Harrell's C statistic was calculated for death, introducing significant unadjusted clinical and analytical parameters on admission. Note that when diabetes mellitus (DM) was added to the model, adjusted Harrell's C statistic was not modified. Maxima adjusted Harrell's C statistic was obtained when HOMA2-IR>2.2 was introduced (0.967; CI 95%= 0.946-0.989).
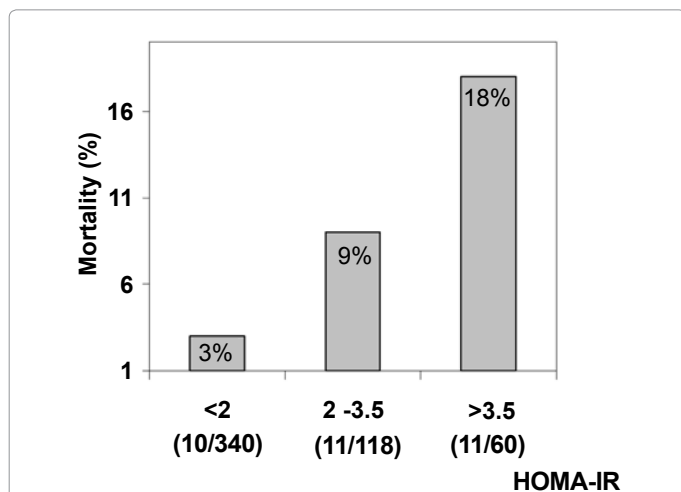
Figure 1: In-hospital mortality and Insulin Resistance. The incidence of mortality grows contemporary to the increasing of insulin resistance. Insulin Resistance <2 had a in-hospital mortality of 3% (10/340) meanwhile higher mortality was observed in patients with insulin resistance >3.5 (18%) (11/60). Patients with IR 2-3.5 had an intermediate mortality (9%) (11/118).
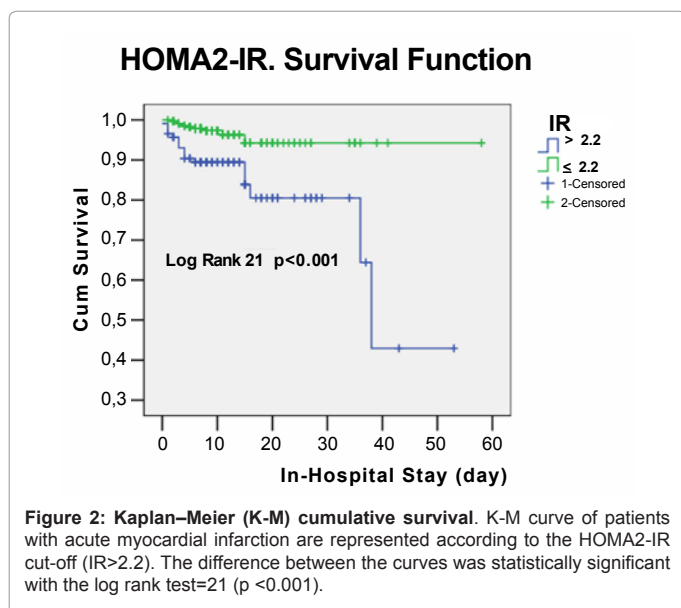
Figure 2: Kaplan–Meier (K-M) cumulative survival. K-M curve of patients with acute myocardial infarction are represented according to the HOMA2-IR cut-off (IR>2.2). The difference between the curves was statistically significant with the log rank test=21 (p <0.001).
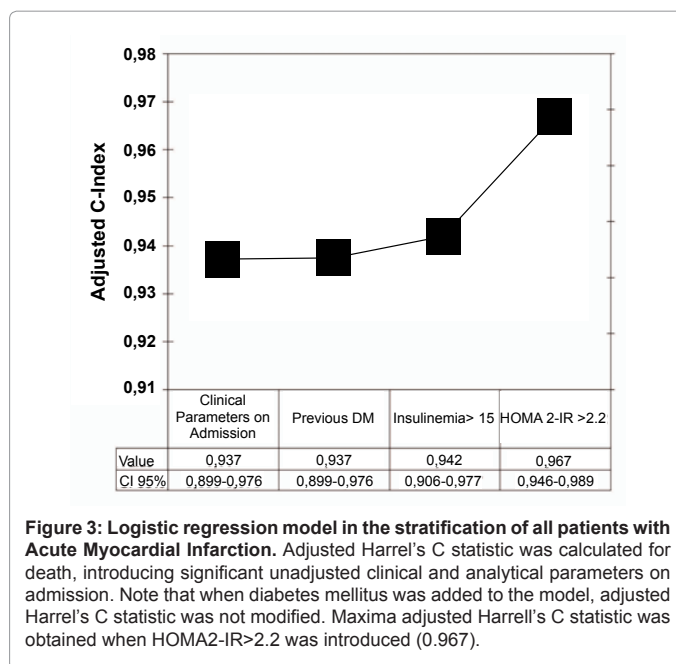
Figure 3: Logistic regression model in the stratification of all patients with Acute Myocardial Infarction. Adjusted Harrel's C statistic was calculated for death, introducing significant unadjusted clinical and analytical parameters on admission. Note that when diabetes mellitus was added to the model, adjusted Harrel's C statistic was not modified. Maxima adjusted Harrel's C statistic was obtained when HOMA2-IR>2.2 was introduced (0.967).

Variable	HR (95% CI)	P-value
Aged >70 years	3.2 (1.04-10)	0.04
Killip>1	4 (1.4-14)	0.012
LogHOMA2-IR (IR≥2)	3.4 (1.2-9)	0.017

CI: confidence interval; HR: hazard ratio

Table 2: Multivariate Logistic Regression Predictors of Mortality in Patients with Acute Myocardial Infarction.

At multivariable backward linear regression analysis, HOMA2-IR>2.2 was an independent predictor of in-hospital mortality (Hazard Ratio=3.4; 1.2-9) (p=0.017) in addition to aged >70 years (Hazard Ratio =3.2; 1.04-10) (p=0.04) and Killip class >1 (Hazard Ratio =4; 1.4-14) (p=0.012) (Table 2).

Discussion

The main finding of the present investigation is that mortality rate correlated to the HOMA2-IR index in patients with acute myocardial infarction. Moreover, patients with elevated IR have a higher incidence of previous metabolic and cardiovascular events. Therefore, IR may play a short-term prognostic role in patients with AMI.

Homeostatic Model Assessment (HOMA) is a surrogate index widely used to study the role of insulin sensitivity or resistance, not time-consuming and that has been compared with a number of well-validated methods including hyperinsulinemic-euglycemic clamp method, the gold standard for measuring insulin sensitivity [6,8]. The HOMA model was first described in 1985 [7] and has been recently updated with some physiological adjustments to a computer version providing a more accurate index [9,20].

IR is known to be part of the glycometabolic response to stress but identification of IR cut-off, and its clinical relevance in the early phase of AMI has been controversial. Nishio et al. [10] observe IR (cut-off <2) in 47/61 patients (77%) and identified two different subgroups among non-diabetic patients: the transient IR group which correlated with stress hormones, and the continuous or persistent IR that was found to be a predictor of early restenosis after coronary stenting. Criteria

used by Lazzeri et al. [11] for the definition of IR were in accordance with the published guidelines proposed by European Group of the study of IR (EGIR) and it was present in 52.9% of patients with STEMI submitted to percutaneous coronary intervention. Caccamo G et al. [12] observed IR>2 in 56% in non-diabetic patients with Acute Coronary Syndrome; they calculated HOMA1-IR index according to the Matthews' formula and did not find correlation between high levels of HOMA-IR and intra-hospital global mortality. Our group used the model HOMA2-IR updated with some physiological adjustments to a computer version because in our institution, it has been used in longitudinal and epidemiological studies [21]. In according to these methodological problems the use of HOMA to make comparisons across different groups may be difficult and uncorrected. HOMA values are rarely normally distributed and should therefore be logarithmically transformed and reported with appropriate measures of dispersion. Moreover, HOMA sensitivity from a normoglycemic or hiperglycemic population in each comparative group should be established first in order to determine whether a difference in IR between groups simply reflects a difference baseline.

The pathophysiologic mechanism underlying the association between IR, hyperglycaemia and mortality in patients with AMI is not fully understood. Lazzeri C et al. [22] observed that insulin secretion in the early phase of non-diabetic ST-elevation myocardial infarction is strictly related to body mass index and was an independent predictor for intra-intensive cardiac unit mortality. More recently, Garcia et al. [23] observed that hyperinsulinaemia was the most important factor associated with the occurrence of new cardiovascular events at long-term follow-up in Colombian patients with acute myocardial infarction, thus emphasizing the prognostic role of insulin resistance even at long term.

The fact that IR was a prognostic indicator in our patients, additive to admission clinical factors (hypertension, BMI, Killip class, STEMI vs NSTEMI) and that we have not found correlation between CK-MB and IR, suggest that it could be an important outcome factor, rather than a simple consequence of a larger or smaller infarct size. The number of coronary artery affected was higher in patients with IR>2.2 (1.9±1) than in those with an IR≤2 (1.42±0.8), what could influence in increasing in hospital mortality.

Furthermore, more than 88% of our patients underwent a percutaneous coronary intervention. It is known that hyperglycaemia and/or hyperinsulinaemia in the acute stage of myocardial infarction are predictors of impaired coronary flow, both before and after reperfusion therapy with the occurrence of a non-reflow phenomenon after angioplasty [24-26].

It is speculated that this acute endothelial dysfunction could attenuate the endothelium dependent vasodilatation, abolish the effect of ischemic preconditioning and induce oxidative stress affecting platelet function, coagulation and fibrinolysis [27,28].

It is difficult to explain the role of DM in the outcomes of these patients. Mortality in DM patients was higher in univariate analysis than in patients without DM (10% vs 4%) but this cardiovascular factor did not modify the probability of dying when it was added to the logistic regression model (Harrell's C model) (Figure 3). The definition of stress hyperinsulinaemia is intrinsically difficult in patients with DM because these patients are more likely to receive insulin and/ or oral anti-diabetic drugs before experiencing an AMI [3,4]. In our protocol, all diabetic patients with hyperglycaemia in the acute phase of AMI were treated with short-acting insulin according to digital

glycemia test [29]. Plasma insulin and C-peptide concentration were analyzed in fasting samples taken on the first morning after admission (12 h after the last prescribed dose of insulin).Patients who required a continuous infusion of insulin were excluded from our study because it must be remembered that any increase in HOMA following initiation of treatment simply reflects the mechanism of action of the drug. However, we cannot exclude, that the use of HOMA to assess insulin sensitivity in subjects treated with intermittent insulin would have some potential problems that could have modified our results.

Limitations

Some potential problems need further validation. The possibility of bias selection and/or residual confounding from unknown or unmeasured covariates cannot be excluded resulting in attenuation or inflation of the odds ratios (type 1 or type 2 errors). Such issues are inherent limitations of observational cohort studies.

We assess insulin sensitivity in fasting samples taken on the first morning after admission but insulin resistance is initially a postprandial disturbance and usually, when basal disturbance appears, the process has been in progress of some time.

Clearly HOMA is more convenient for the subject than clamp techniques, but the sensitivity of the technique for detecting metabolic abnormalities is lower, as post-load insulin and glucose concentrations are not included in the calculation. HOMA has the important limitation because it assumes that hepatic and peripheral insulin sensitivity is equal, which is not certain.

The use of HOMA in subjects treated with intermittent insulin needs further validation.

Conclusions

This study shows a high association between HOMA2-IR on admission and mortality rate in patients with AMI. Beyond traditional cardiovascular risk factors, insulin resistance seems to have an important prognostic role in patients with AMI.

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