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Chiara Lazzeri, Serafina Valente, Marco Chiostrì,
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Abstract

The relationship between insulin secretion and acute insulin resistance (as assessed by Homeostatic Model Assessment [HOMA] index) and clinical and biochemical parameters in the early phase of non-diabetic ST-elevation myocardial infarction (STEMI) is so far unexplored. We aimed at assessing this relation in 286 consecutive STEMI patients without previously known diabetes submitted to primary percutaneous coronary intervention (PCI). Insulin resistance (as indicated by HOMA) was detectable in 67.1%. Non-parametric correlation showed that HOMA index was significantly correlated with BMI ($r = 0.242$; $p < 0.0001$) and HbA_{1c} ($r = 0.189$; $p < 0.001$). At multivariable backward linear regression analysis, glycaemia was directly related to leukocyte count ($p = 0.0003$), age ($p = 0.0001$), creatine kinase isoform MB (CK-MB) ($p = 0.00278$) and lactate ($p < 0.0001$). Insulin was directly and significantly related to glycaemia ($p = 0.0006$), body mass index (BMI) ($p = 0.00028$) and lactate ($p = 0.0096$). In the early phase of STEMI without previously known diabetes the acute glucose dysmetabolism is quite complex, comprising increased glucose values and the development of acute insulin resistance. While insulin secretion is strictly related to BMI, apart from glucose levels, increased glucose values can be mainly related to the acute inflammatory response (as indicated to leukocyte count and C-RP), to age and to the degree of myocardial damage (as inferred by CK-MB).

Keywords

Acute insulin resistance, acute phase, HOMA index, hyperglycaemia, STEMI

Introduction

In the setting of acute myocardial infarction (MI),¹ hyperglycaemia is not simply a marker of pre-existing diabetes or glucose intolerance but part of the stress response to myocardial injury mainly related to acute catecholamine release.^{2,3}

In patients with ST elevation myocardial infarction (STEMI) hyperglycaemia is common and, though frequently untreated, associated with an increased risk of death.^{4–7} In these patients, increased glucose values hold a prognostic role when measured not only on admission⁴ but also throughout hospital stay.^{8–11} We recently¹² observed that, in non-diabetic STEMI patients, the poorer in-hospital glucose control was associated with higher mortality; peak glycaemia >180 mg/dl was associated with the highest mortality, whereas patients with peak glycaemia between 140 and 180 mg/dl exhibited intermediate mortality rates.

In the acute phase of STEMI, increased glucose levels have been related to the extent of myocardial injury and to the stress inflammatory response, but data on this topic are scarce and controversial.

Insulin resistance is known to be part of the glycometabolic response to stress, but few studies assessed the

role of insulin resistance, evaluated by means of Homeostatic Model Assessment (HOMA) index, in the early phase of acute myocardial infarction.^{13,14} In non-diabetic STEMI patients submitted to percutaneous coronary intervention (PCI), we reported that insulin resistance, as assessed by HOMA-index, is quite common and helps in the early risk stratification, since it represents an independent predictor for in-hospital mortality.¹⁵ More recently, Garcia *et al.*¹⁶ observed that hyperinsulism 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 emphasising the prognostic role of insulin resistance even at long term.

Intensive Cardiac Coronary Unit, Heart and Vessel Department,
Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Corresponding author:

Chiara Lazzeri, MD, Intensive Cardiac Care Unit, Heart and Vessel
Department, Viale Morgagni 85, 50134 Florence, Italy.
Email: lazzeric@libero.it

The relationship between insulin secretion and acute insulin resistance (as assessed by HOMA index) and clinical and biochemical parameters in the early phase of non-diabetic STEMI is so far unexplored; we aimed to assess this relation in 286 consecutive STEMI patients without previously known diabetes submitted to primary PCI.

Study population

From 1 January 2008 to 31 December 2009, 286 consecutive patients with STEMI (within 12 hours of symptoms' onset) and without previously known diabetes were admitted to our Intensive Cardiac Care Unit (ICCU), which is located at a tertiary centre. In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI.^{11,14,15-18} STEMI patients are first evaluated by the Medical Emergency System staff in the pre-hospital setting and then directly admitted to the catheterisation laboratory or transferred to it after a rapid stabilisation in First Aid. After primary PCI, they are admitted to our ICCU.

A successful procedure was defined as an infarct artery stenosis <20% associated with TIMI (Thrombolysis In Myocardial Infarction) grade 3 flow. Failure PCI was defined as resulting in TIMI grade 0 to 2 flow, regardless of the residual stenosis.¹⁹

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association.²⁰

On ICCU admission, after PCI, in a fasting blood sample the following parameters were measured: glucose (mg/dl), troponin I (ng/ml), insulin (mU/L), uric acid (mg/dl), C-reactive protein (C-RP, mg/dl) (normal values <9), alanine aminotransferase (ALT), aspartate amino transferase (AST), gamma-glutamyl transferase (GGT) NT-pro brain natriuretic peptide (NT-BNP, pg/ml),¹⁶ total cholesterol (mg/dl), triglycerides (mg/dl), HDL, thyroid stimulating hormone (TSH, pg/ml) and fibrinogen (mg/dl). Creatinine (mg/dl) was also measured in order to calculate glomerular filtration rate (ml/min/1.73 m²).²¹ Glucose, Tn I, ALT and AST were measured three times per day during ICCU-stay and peak values for each variable were considered.

Transthoracic two-dimensional echocardiography was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF).

Definition of insulin resistance

Criteria used for the definition of insulin resistance are in accordance with the recently published guidelines proposed by the European Group of the study of Insulin Resistance (EGIR).²² HOMA was calculated according to the following formula: {[fasting insulin (μU/ml)] × [fasting glucose (mmol/L)]}/22.5. Subjects whose values exceeded the sex-specific 75th percentile (i.e. 1.80 for females and 2.12 for

Table 1. Clinical characteristics of patients included in the study.

| | Median (25th–75th percentile) or frequency (%) |
|---|--|
| Age (years) | 65 (57–75) |
| Males/females | 215/71 (75.2/24.8%) |
| History of: | |
| Smoking, n (%) | 186 (65.0%) |
| COPD | 21 (7.3%) |
| Previous PCI | 33 (11.5%) |
| Previous AMI | 35 (12.2%) |
| Hypertension | 117 (40.9%) |
| Estimated GFR (ml/min per 1.73 m ²) | 84.9 (69.2–102.9) |
| AMI location | |
| Anterior | 155 (54.2%) |
| Inferior | 114 (39.9%) |
| Other | 17 (5.9%) |
| Coronary artery disease | |
| 1-vessel | 121 (42.3%) |
| 2-vessel | 89 (31.1%) |
| 3-vessel | 76 (26.6%) |
| LM | 18 (6.3%) |
| CABG | 2 (0.7%) |
| PCI failure | 14 (4.9%) |
| EF (%) | 45 (35–50) |
| Latency (minutes) | 210 (160–322) |
| Drugs on admission | |
| Clopidogrel | 98.2 (281/286) |
| Unfractionated heparin | 88.8 (254/286) |
| IIa/IIb glycoprotein inhibitors | 74.8 (214/286) |
| Nitrates | 68.2 (195/286) |
| Betablockers | 62.2 (178/286) |
| ACE-inhibitors/ARB | 87.1 (249/286) |
| Statins | 94.1 (269/286) |
| Inotropes | 9.8% (28/286) |
| In-hospital mortality | 11 (3.8%) |

COPD: chronic obstructive pulmonary disease, PCI: percutaneous coronary intervention, MI: myocardial infarction, GFR: glomerular filtration rate, LM: left main coronary artery, EF: ejection fraction, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blockade

males) were considered to have insulin resistance (HOMA-IR).^{15,23} The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained in all patients before enrolment.

Statistical analysis

Data have been entered in a dedicated database and processed by means of SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). A two-tailed *p*-value <0.05 was

Table 2. Comparison between patients with and without HOMA positivity.

| | HOMA positivity n=192 (67.1%) | HOMA negativity n=94 (32.9%) | p-value Mann-Whitney U-test or Fisher's exact test or χ^2 |
|--|----------------------------------|---------------------------------|--|
| Males/females | 146/46 (76.0/24.0%) | 69/25 (73.4/26.6%) | 0.663 |
| Age (years) | 66 (56–75) | 64 (57–76) | 0.714 |
| BMI (kg/m ²) | 26.3 (24.5–28.0) | 25.1 (23.1–27.0) | <0.001 |
| Estimated GFR (ml/min per 1.73m ²) | 81.8 (66.0–101.4) | 87.7 (73.1–106.8) | 0.060 |
| AMI location | | | |
| Anterior | 110 (57.3%) | 45 (47.9%) | 0.304 |
| Inferior | 72 (37.5%) | 42 (44.7%) | |
| Other | 10 (5.2%) | 7 (7.4%) | |
| Killip class | | | |
| I | 157 (81.8%) | 78 (83.0%) | 0.849 |
| II | 17 (8.8%) | 6 (6.4%) | |
| III | 5 (2.6%) | 2 (2.1%) | |
| IV | 13 (6.8%) | 8 (8.5%) | |
| EF (%) | 42 (35–50) | 45 (37–52) | 0.168 |
| PCI failure | 12 (6.3%) | 2 (2.1%) | 0.154 |
| Mortality | 6 (3.1%) | 5 (5.3%) | 0.350 |
| Glucose (mg/dl) | 138 (116–166) | 111 (99–130) | <0.001 |
| Peak glucose (mg/dl) | 154 (133–187) | 130 (114–153) | <0.001 |
| HbA _{1c} >6.5% | 27 (14.1%) | 6 (6.4%) | 0.075 |
| Tn I (ng/ml) | 107.3 (53.0–209.5) | 61.6 (21.9–157.2) | 0.002 |
| NT-proBNP (pg/ml) | 1253 (400–3,206) | 1241 (529–2,505) | 0.732 |
| Uric acid (mg/dl) | 5.6 (4.7–6.8) | 5.4 (4.2–6.2) | 0.053 |
| ESR (mm/h) | 22 (13–37) | 24 (12–42) | 0.865 |
| Leucocytes (counts/ml) | 11875 (9,320–14,670) | 10375 (8,602–12,545) | 0.001 |
| CRP positivity | 99 (51.6%) | 58 (61.7%) | 0.129 |
| Fibrinogen (mg/dl) | 378 (325–466) | 383 (329–448) | 0.778 |
| ALT (U/L) | | | |
| Admission | 44 (28–82) | 31 (18–50) | <0.001 |
| Peak | 64 (44–101) | 41 (25–90) | <0.001 |
| Discharge | 37 (28–54) | 30 (18–45) | 0.003 |
| AST (U/L) | | | |
| Admission | 90 (47–200) | 57 (29–115) | <0.001 |
| Peak | 248 (135–416) | 128 (68–314) | <0.001 |
| Discharge | 60 (35–98) | 46 (33–74) | 0.059 |
| GGT (U/L) | 32 (22–63) | 24 (17–46) | 0.004 |
| Cholesterol (mg/dl) | 199 (166–229) | 186 (159–204) | 0.004 |
| HDL(mg/dl) | 41 (36–49) | 40 (35–45) | 0.120 |
| LDL(mg/dl) | 134 (102–156) | 124 (100–140) | 0.015 |
| Triglycerides (mg/dl) | 98 (77–146) | 92 (70–124) | 0.159 |
| TSH (mU/l) | 0.93 (0.43–1.55) | 1.00 (0.56–1.80) | 0.166 |

HOMA: Homeostatic Model Assessment, BMI: body mass index, GFR: glomerular filtration rate, AMI: acute myocardial infarction, EF: ejection fraction, PCI: percutaneous coronary intervention, NT-pro-BNP, N terminal pro-brain natriuretic peptide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: alanine amino transferase, ASP: aspartate amino transferase, GGT: gamma glutamyl transferase, TSH: thyroid stimulating hormone

Table 3. Comparison between patients with and without HOMA positivity after exclusion of patients with glycated Hb >6.5%.

| | HOMA positivity n=165 (65.2%) | HOMA negativity n=88 (34.8%) | p-value Mann–Whitney U-test or Fisher's exact test |
|--------------------------|----------------------------------|---------------------------------|--|
| BMI (kg/m ²) | 26.3 (24.5–27.7) | 25.1 (22.9–27.0) | <0.001 |
| Glucose (mg/dl) | 131 (114–158) | 111 (99–126) | <0.001 |
| Peak glucose (mg/dl) | 148 (131–179) | 128 (113–150) | <0.001 |
| Tn I (ng/ml) | 107.0 (52.6–218.0) | 60.9 (21.6–155.6) | 0.002 |
| Leucocytes (counts/ml) | 11,730 (9,320–14,700) | 10,420 (8,640–12,650) | 0.005 |
| CRP positivity | 82 (49.7%) | 55 (62.5%) | 0.064 |
| ALT (U/L) | | | |
| Admission | 43 (29–84) | 31 (18–50) | <0.001 |
| Peak | 65 (44–102) | 41 (25–90) | <0.001 |
| Discharge | 38 (28–55) | 30 (18–45) | 0.002 |
| AST (U/L) | | | |
| Admission | 85 (41–199) | 59 (29–116) | 0.002 |
| Peak | 255 (134–415) | 128 (68–314) | <0.001 |
| Discharge | 59 (35–102) | 44 (33–74) | 0.063 |
| GGT (U/L) | 31 (22–64) | 23 (16–42) | 0.002 |
| Cholesterol (mg/dl) | 203 (169–233) | 187 (160–206) | 0.007 |
| LDL(mg/dl) | 137 (105–159) | 125 (103–141) | 0.020 |

HOMA: Homeostatic Model Assessment, BMI: body mass index, CRP: C-reactive protein, AST: alanine amino transferase, ASP: aspartate amino transferase, GGT: gamma glutamyl transferase, TSH: thyroid stimulating hormone

considered statistically significant. Data of insulin resistance subgroups are reported as frequencies (percentages) and medians (25th–75th percentile) and were analysed by Fisher's exact test (categorical variables) and Mann–Whitney U-test (continuous variables, which resulted in almost all non-normally distributed). Correlations between insulin resistance, as assessed by HOMA index, and clinical, procedural and biochemical data have been investigated in a univariable way by means of Spearman's rho. A linear regression analysis investigated the correlation insulin versus glycaemia. By means of two multivariable backward linear regression analyses we explored the adjusted correlations of glycaemia and, respectively, insulinaemia, with clinical and biochemical variables and the respective final models have been reported. The initial model was constructed choosing as candidate variables those that significantly differed between subgroups or were known to be clinically relevant. A backward stepwise linear regression analysis was performed, after assessing for linearity, in order to find predictors for in-ICCU mortality. The stepwise procedure (performed using a probability of the likelihood ratio test <0.05 for inclusion and <0.10 for exclusion) ran until all of the remaining candidate variables resulted significantly related to the outcome. Hagelkerke R^2 and Hosmer–Lemeshow goodness-of-fit test are also reported.

Results

Table 1 shows the clinical characteristics of patients included in the study. Males were prevalent (75.2%). Anterior myocardial infarction was the most frequent location (54.2%). The incidence of PCI failure was 4.9% while in-ICCU mortality rate was 3.8%.

As depicted in Table 2, insulin resistance (as indicated by HOMA positivity) was detectable in 67.1%. Patients with insulin resistance showed a higher BMI ($p < 0.001$) and higher values of admission glucose, peak glucose, Tn I, leucocytes and GGT (<0.001 , <0.001 , $p = 0.002$, $p = 0.001$ and $p = 0.004$ respectively). No difference was detectable between subgroups in HbA_{1c}. Liver transaminases (ALT and AST) were significantly higher in insulin-resistant patients on admission, during ICCU stay and at discharge. In-ICCU mortality rate was comparable while the incidence of PCI failure showed a trend which did not reach statistical significance. Patients with HOMA positivity exhibited higher values of total cholesterol ($p = 0.004$) and LDL ($p = 0.015$). Table 3 shows the comparison between patients with insulin resistance and those without, after exclusion of patients with HbA_{1c} >6.5% (33 patients, 11.5%); only parameters which were significantly different were reported. Patients with insulin resistance exhibited a higher BMI ($p < 0.001$) and higher values of admission glucose, peak glucose, Tn I,

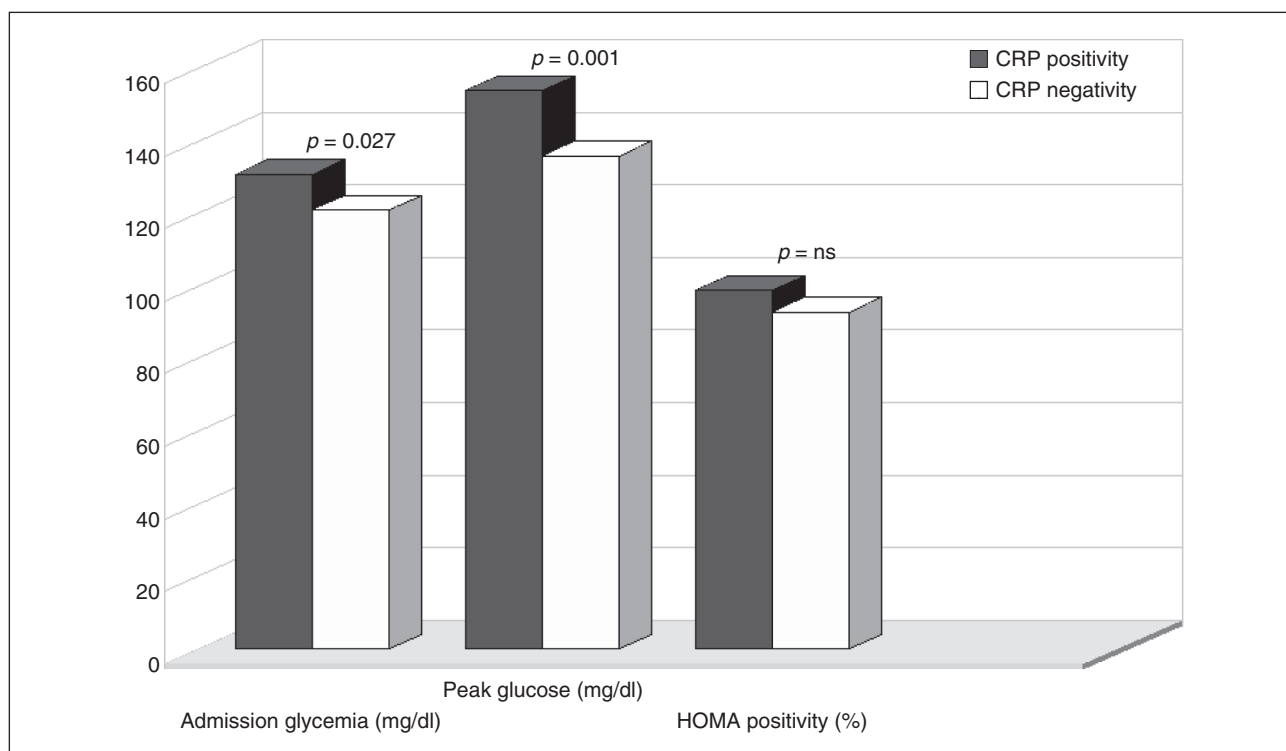


Figure 1. Comparison between patients with and without C-RP positivity.
CRP: C-reactive protein, HOMA: Homeostatic Model Assessment

leukocytes and GGT (<0.001 , <0.001 , $p = 0.002$, $p = 0.005$ and $p = 0.002$ respectively). In this subgroup, higher levels of total and LDL cholesterol were observed ($p = 0.007$ and $p = 0.020$, respectively). Liver transaminases (ALT and AST) were significantly higher in insulin-resistant patients on admission, during ICCU stay and at discharge.

In our series, C-RP positivity was present in 157 patients (157/286, 54.9%). As shown in Figure 1, patients with C-RP positivity showed significantly higher values of admission and peak glucose ($p = 0.027$ and $p = 0.001$ respectively) in the lack of differences in HOMA positivity.

Linear regression analysis (Figure 2) showed that in our series admission glycaemia was directly and significantly correlated with insulin values ($p < 0.001$).

Non-parametric correlation (Spearman's rho) showed that HOMA index was significantly correlated with BMI ($r = 0.242$; $p < 0.0001$) and HbA_{1c} ($r = 0.189$; $p < 0.001$).

At multivariable backward linear regression analysis (Table 4), glycaemia was directly related to leukocyte count ($p = 0.0003$), age ($p = 0.0001$), creatine kinase isoform MB (CK-MB) ($p = 0.00278$) and lactate ($p < 0.0001$). Insulin was directly and significantly related to glycaemia ($p = 0.0006$), BMI ($p = 0.00028$) and lactate ($p = 0.0096$).

At multivariable linear regression analysis the following variables were independently associated with in-ICCU

mortality: eGFR (1 ml/min per 1.73m² step) (OR 0.96; 95% confidence interval [CI] 0.91–1.00; $p = 0.052$), PCI failure (OR 9.00; 95% CI 1.06–76.4; $p = 0.044$), TnI (1 ng/ml step) (OR 1.003; 95% CI 1.000–1.006; $p = 0.031$) and admission glycaemia (1 mg/ml step) (OR 1.02; 95% CI 1.006–1.029; $p = 0.002$). Hosmer–Lemeshow goodness-of-fit χ^2 : 2.850; $p = 0.943$. Hagelkerke R square: 0.538.

Discussion

The main finding of the present investigation is that, in acute phase of STEMI patients without previously known diabetes submitted to mechanical revascularisation, insulin secretion is strictly related to BMI, apart from glucose levels. Also, increased glucose values can be mainly related to the acute inflammatory response (as indicated to leukocyte count and C-RP), to age and to the degree of myocardial damage (as inferred by CK-MB).

Data on insulin secretion in acute myocardial infarction are scarce, conflicting and mainly concerning the pre-thrombolytic and thrombolytic era. While some studies documented a failure of insulin response following acute myocardial infarction,^{3,24,25} others reported that plasma insulin is high in this setting.^{25,26} Interestingly, insulin values were related to infarct size in MI patients not submitted

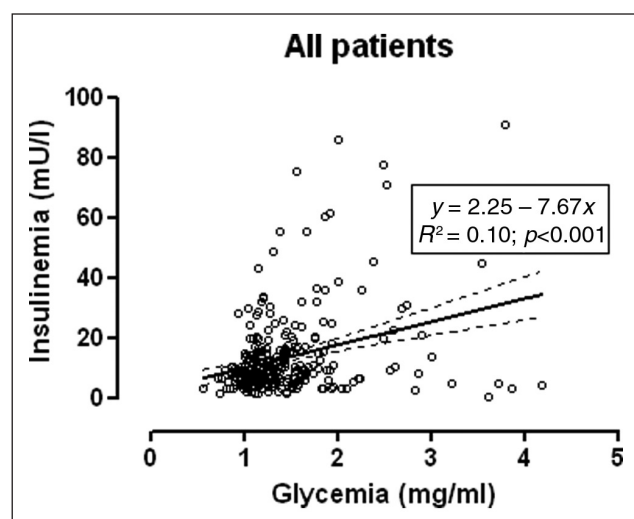


Figure 2. Correlation between insulin and glucose values in all STEMI patients included in the study.

to reperfusion,²⁷ whereas this relation was not detectable in patients submitted to thrombolysis.²⁶ In the era of mechanical reperfusion, Nishio *et al.*¹³ identified, by means of HOMA index, two different subgroups among 61 non-diabetic MI patients: the non-insulin resistant group and the insulin resistant (IR) group, which consisted of transient IR, which correlated with stress hormones, and continuous IR, which correlated with leptin (associated with endothelial dysfunction) thus contributing to restenosis after coronary stenting at four-month follow-up. In our investigation (including 286 non-diabetic STEMI patients), BMI is related to insulin secretion and to the development of acute insulin resistance, as indicated by HOMA positivity. Moreover, insulin resistant patients showed an impairment of liver function as indicated by higher transaminases (both on admission and at discharge) and higher values of total cholesterol. According to our data, non-diabetic STEMI patients who develop acute insulin resistance in the early phase share some common features with chronic insulin resistance,²⁸ such as the relation with BMI and the association with liver impairment (as inferred by increased transaminases) and increased cholesterol values. However, the underlying mechanisms of acute insulin resistance in the early phase of STEMI after revascularisation are far from fully understood and the management of these patients has not been defined.

On the other hand, according to our results, there are three main factors affecting glucose levels in the acute phase of non-diabetic STEMI submitted to PCI: the degree of the inflammatory response, the extent of myocardial damage, and age, which, together, can contribute a strong prognostic role of hyperglycaemia for early mortality in

Table 4. Multivariable linear regression analysis.

| | Outcome: glycaemia | | | |
|-----------------|----------------------|---------------|----------------------|---------|
| | Absolute coefficient | CI (95%) | Standard coefficient | p-value |
| Lactate | 0.101 | 0.066–0.0136 | 0.356 | <0.0001 |
| Leukocyte count | 0.029 | 0.014–0.045 | 0.233 | 0.0003 |
| Age | 0.010 | 0.005–0.015 | 0.232 | 0.0001 |
| CK-MB | 0.0003 | 0.0001–0.0005 | 0.144 | 0.0278 |
| Constant | 0.15 | –0.25–0.54 | | 0.46 |
| | Outcome: insulin | | | |
| | Absolute coefficient | CI (95%) | Standard coefficient | p-value |
| Glycaemia | 6.4560 | 2.80–10.12 | 0.263 | 0.0006 |
| BMI | 0.7770 | 0.271–1.283 | 0.200 | 0.0028 |
| Lactate | 1.3590 | 0.334–2.384 | 0.2 | 0.0096 |
| Constant | –20.6 | –37.8 | –3.47 | 0.0187 |

CK-MB: creatine kinase isoform MB, BMI: body mass index

STEMI patients.⁴ The relation between hyperglycaemia and inflammation has been previously described in healthy subjects^{29,30} and in critically ill patients.³¹ In patients with acute myocardial infarction, hyperglycaemia, measured on hospital admission, was associated with increased inflammatory markers (C-RP and IL-18), enhanced cytotoxic T-cell activity and reduced expression of T cells implicated in the limitation of the immune process, thus increasing immune stimulation.³² We recently observed that glucose values, measured after mechanical revascularisation, were associated with the inflammatory response.¹¹

The relationship between hyperglycaemia and infarct size is controversial, with some studies showing no or weak correlation.^{3,33} On the other hand, in previous studies by others^{34–36} and us,¹¹ infarct size, measured by enzymatic methods (CPK and CPK-MB) and by troponin I, was larger in STEMI patients with hyperglycaemia compared with those without. Recently,³⁷ in STEMI patients treated with PCI, hyperglycaemia on admission was associated with larger infarct size determined by SPECT, and hyperglycaemia itself was an independent predictor of infarct size when adjusted for confounding variables (i.e. sex and age). Multiple physiological studies demonstrated that hyperglycaemia may have a direct detrimental effect on ischemic myocardium through a variety of mechanisms (such as decreasing collateral circulation³⁸ and promoting apoptosis³⁹). On the other hand, excessive stress-mediated release of counter-regulatory hormones (i.e. catecholamines and glucagon) caused by a greater degree of myocardial damage can account, at least in part, for the extent of hyperglycaemia⁴⁰

Few data are so far available on the ‘age effect’ on glucose metabolism in the early phase of acute myocardial

infarction. Kosiborod *et al.*⁵ observed that elevated glucose is associated with increased mortality in elderly acute myocardial infarction and our group recently reported²³ that older STEMI patients showed the highest glucose levels and the poorest glycaemic control during ICCU stay in the lack of differences in insulin resistance incidence. These finding were confirmed after exclusion of patients with poor glycaemic control in the previous 2–3 months (that is, patients with HbA1c >6.5%). We supposed that the higher glucose values after myocardial injury observed in elderly STEMI patients could probably be related (beyond the age effect on beta cell mass and sensitivity) to the age-related differences in pancreatic and/or hepatic sensitivity to β -adrenergic signals.^{41,42} The present investigation further confirms these finding by documenting that glucose values are significantly related to age.

In conclusion, in early phase STEMI patients without previously known diabetes, the acute glucose dysmetabolism is quite complex, comprising increased glucose values and the development of insulin resistance. While insulin secretion and acute insulin resistance can be strictly related to BMI, the degree of inflammatory activation, myocardial damage, and age are able to influence glucose values in the early phase of non-diabetic STEMI submitted to mechanical revascularisation. Further studies are needed to establish whether acute insulin resistant STEMI patients deserve a different (more aggressive) treatment.

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Conflict of interest statement

No conflict of interest.

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