Letter to the Editor

Insulin resistance and short-term mortality in patients with acute myocardial infarction

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Homeostatic Model Assessment (HOMA) is a useful model for the evaluation of insulin resistance (IR) in individuals with glucose intolerance, mild to moderate diabetes, and other insulin-resistant conditions [1]. 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 (AMI).

This was a single-centre observational prospective study. We studied 518 subjects, 361 (75%) males, all referred to our Coronary Care Unit for AMI. All patients with no specific contraindications received the recommended drugs in the acute phase. Patients with a fasting glucose level <110 mg/dL and without a history of diabetes mellitus (DM) were classified as normoglycemic.

Plasma insulin and C-peptide concentration were analysed 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 and an Elesys 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.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

Continuous variables were expressed as mean ± standard deviation or standard error of mean, determining the differences between groups by Student’s t-test. The categorical variables were compared by chi-square analysis. ROC curve analysis was used to assess the ability of various levels of HOMA2-IR to predict mortality. The model’s discriminative ability was assessed with the Harrell’s C statistic. A p-value of <.05 was considered statistically significant for all analyses. Data were analysed using the Statistical Package for Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA).

The median age of our sample was 65 (30–95) years, 75% were males. STEMI was observed in 63% (329/518 of patients) and thrombotic therapy was administered in 35% (115/329 of STEMI patients) of patients. Percutaneous coronary interventions were 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 the hospital after a median of 8 days (range 1–36 days).

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%) and 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).

Subjects were divided into two groups according to HOMA index value (Table 1): 1) patients at elevated HOMA > 2.2 and 2) patients at low HOMA ≤ 2.2 which represent the control group. Insulin resistance (IR > 2.2) was detectable in 27% (140/518 patients) and was associated with previous cardiovascular diseases, hypertension, diabetes, metabolic syndrome and with a number of affected coronary arteries higher than in those with an IR ≤ 2 (1.9 ± 1 vs. 1.42 ± 0.8) (p < 0.001).

In-hospital mortality was 6% (32/518 of patients). The incidence of mortality grows contemporary to the increase of HOMA: IR < 2 had an in-hospital mortality of 3% (10/340) meanwhile higher mortality was observed in patients with IR > 3.5 (18%) (11/60). Patients with IR of 2–3.5 had an intermediate mortality (9%) (11/118). Moreover, patients with IR > 2.2 exhibited a 2.7-fold increase of mortality than those with IR ≤ 2.2 in unadjusted analysis (Table 1). In Fig. 1 we can observe a 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

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statistic was obtained when HOMA2-IR > 2.2 was introduced (0.967; CI 95% = 0.946–0.989).

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 age ≥ 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).

The main finding of the present investigation is that in acute phase of myocardial infarction, the higher the HOMA2-IR on admission the higher the mortality is. Our group used the HOMA2-IR updated with some physiological adjustments to a computer version because in our institution, it has been used in longitudinal and epidemiological studies [2].

Insulin resistance (IR > 2.2) was detectable in 48% of our patients with diabetes and 29% in non-diabetes patients, lower than that observed by Nishio et al. [3] (77%) and Caccamo et al. [4] (56%) and higher than that observed by Lazzeri et al. [5] (5%).

The pathophysiological mechanism underlying the association between IR, hyperglycaemia and mortality in patients with AMI is not fully understood [6,7]. The fact that IR was a prognostic indicator in our patients, additive to admission clinical factors and that we have not found a correlation between CK-MB and IR, suggests that it could be an important outcome factor, rather than a simple consequence of a larger or smaller infarct size. The number of coronary arteries affected was higher in patients with IR > 2.2 which could influence hospital mortality. Furthermore, it is known that stress hyperglycaemia and/or hyperinsulinaemia in the acute stage of myocardial infarction are predictors of high risk ventricular tachyarrhythmia’s [8] and impaired coronary flow with the occurrence of a non-reflow phenomenon after angioplasty [9,10].

It is difficult to explain the role of DM in the outcomes of these patients. DM did not modify the probability of dying when it was added to the logistic regression model (Harrell’s C model). Stress hyperinsulinaemia is intrinsically difficult to obtain in these patients because they are more likely to receive insulin.

HOMA has the important limitation because it assumes that hepatic and peripheral insulin sensitivities are equal, which is not certain. Moreover, plasma insulin and C-peptide concentrations were analysed 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. Insulin resistance seems to significantly have an important short-term prognostic role in patients with AMI.

### References


### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>HOMA2-IR &gt; 2.2 (140 patients)</th>
<th>HOMA2-IR ≤ 2 (378 patients)</th>
<th>OR (CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>48%</td>
<td>21%</td>
<td>1.8 (1.3–2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73%</td>
<td>61%</td>
<td>1.5 (1.1–2.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>71%</td>
<td>39%</td>
<td>2.7 (2–3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip &gt; 1 (admission)</td>
<td>43%</td>
<td>24%</td>
<td>0.8 (0.6–1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery affected &gt; 1</td>
<td>50%</td>
<td>31%</td>
<td>2.8 (2.1–3.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatine kinase MB (m ± st. error mean)</td>
<td>138 ± 15</td>
<td>32 ± 8</td>
<td>12.5%</td>
<td>0.7</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>15.5%</td>
<td>11.8 ± 9</td>
<td>9.8 ± 6</td>
<td>0.023</td>
</tr>
<tr>
<td>Fasting glycaemia (mg/dL)</td>
<td>160 ± 64</td>
<td>115 ± 37</td>
<td>0.967</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.7 ± 1.4</td>
<td>6 ± 1.2</td>
<td>0.989</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin ([μg/mL])</td>
<td>29 ± 24</td>
<td>8 ± 8</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>5.4 ± 4</td>
<td>3 ± 1.3</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>166 ± 88</td>
<td>135 ± 84</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride &gt; 150 mg/dL</td>
<td>42%</td>
<td>28%</td>
<td>1.56 (1.15–2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Albuminuria/creatininuria*</td>
<td>96 ± 16</td>
<td>62 ± 8</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albuminuria &gt; 20 mg/dL</td>
<td>67%</td>
<td>42%</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Fig. 1

Logistic regression model in the stratification of all patients with acute myocardial infarction. Adjusted Harrell’s C statistic was calculated for in-hospital death, introducing significant unadjusted clinical and analytical parameters on admission. Note that when diabetes mellitus 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).