Hyperinsulinaemia is associated with increased long-term mortality following acute myocardial infarction in non-diabetic patients

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Aims To study the impact of disturbances in glucose metabolism on total mortality in non-diabetic patients with acute myocardial infarction.

Methods and results Four hundred and ninety four patients with a verified myocardial infarction and no history of diabetes were studied. The study population comprised a subgroup of patients screened for participation in the Trandolapril Cardiac Evaluation (TRACE) study. At baseline, fasting insulin, fasting glucose, glycosylated haemoglobin (HbA1c), and urinary albumin excretion were measured. Survival status was determined after 6–8 years. Patients with hyperinsulinaemia were more obese and more frequently suffered from hypertension, previous myocardial infarction and congestive heart failure. In a univariate regression analysis, values in the upper quartile of insulin, glucose, HbA1c, and urinary albumin excretion were associated with an excess mortality risk (RR = 1.8 (1.2–2.7), \( p = 0.002 \); RR = 1.6 (1.2–2.1), \( p = 0.001 \); RR = 1.9 (1.3–2.9), \( p = 0.001 \); RR = 1.6 (1.2–2.1), \( p = 0.02 \) respectively). However, only a high insulin level remained significant in a multivariable analysis (RR = 1.54 (1.03–2.31), \( p = 0.04 \)) including baseline variables, left ventricular systolic function and in-hospital complications.
Introduction

The metabolic syndrome or the insulin resistance syndrome is defined by the World Health Organisation as insulin resistance, impaired glucose tolerance or diabetes— together with at least two of the four conditions of hypertension, dyslipidaemia, obesity or microalbuminuria.1

It is widely believed that the pathophysiological process underlying the clustering of cardiovascular risk factors in the metabolic syndrome is insulin resistance, but the prognostic effect of serum insulin—as a surrogate marker of insulin resistance— in patients with acute myocardial infarction remains to be established.

In the general population, as well as in patients with type 2 diabetes, the prognostic influence of the individual components of the metabolic syndrome is well established. High fasting serum insulin per se precedes and predicts subsequent development of impaired glucose tolerance and type 2 diabetes2 as well as cardiovascular morbidity and mortality.3–5 Fasting glucose levels are positively associated with risk of cardiovascular events even below the diabetic threshold.6 Elevated urinary albumin excretion is not only a well known predictor of nephropathy in diabetes mellitus,7 but also an independent risk factor of cardiovascular disease in both diabetics8 and non-diabetics.9

It is also well known that the presence of diabetes in patients with established coronary heart disease is a marker of further complications.10 However, the importance of these components of the metabolic syndrome is not well studied in patients with coronary heart disease. Therefore, the aim of the present study was to evaluate the impact of fasting serum insulin, fasting plasma glucose, glycosylated haemoglobin (HbA1c) and urinary albumin excretion on long-term prognosis in non-diabetic subjects following acute myocardial infarction.

Methods

Patients

The current study was performed during screening for the Trandolapril Cardiac Evaluation (TRACE) study.11,12 Consecutive patients admitted with an acute myocardial infarction in five coronary care units were enrolled in the current study. A total of 550 patients with enzyme-verified myocardial infarction were included. Four patients died within the first five days, and in four patients the samples intended for insulin and glucose measurements were lost. Forty-eight patients had known diabetes mellitus and were therefore excluded.

Conclusions High fasting plasma insulin is an independent risk factor of all-cause mortality in non-diabetic patients with acute myocardial infarction. This justifies future intervention studies aiming at reducing insulin resistance and using fasting insulin as the target variable.

The Danish Health Authorities as well as the Regional Ethics Committees approved the study. Informed consent was obtained from all participating subjects.

At baseline a medical history was recorded and an echocardiography performed. Left ventricular systolic function was determined by means of the Wall Motion Index.13 Wall Motion Index is closely correlated to left ventricular ejection fraction obtained by radionuclide cardiography or invasive ventriculography.14 At day 2–5 after admission, fasting serum insulin, fasting plasma glucose and HbA1c were measured. A first-voided morning urine sample was collected for albumin determination. The sample was not included if the patient showed signs of urinary tract infection. Congestive heart failure was defined as either history of heart failure requiring continuing diuretic treatment or a Killip class above 1 during hospital admission.

Serum insulin was determined with radio-immunoassay (Compagnie Oris Industrie, S.A., France). Plasma glucose was determined with the glucose-dehydrogenase method and HbA1c was determined with ion exchange chromatography (Bio Rad, Richmond, CA, USA). Urinary albumin concentration was measured with immunoturbidimetry (DAKO, Q328/ NJ, USA).

Statistical methods

Baseline characteristics were compared using the Cochran–Armitage trend test for discrete variables and the Spearman correlation rank test for continuous variables. Mortality curves were generated by means of Kaplan–Meier estimates and differences in mortality were compared using a log rank test. To evaluate the effect on mortality of different levels of insulin, glucose, HbA1c and urinary albumin concentration, relative risks and 95% confidence intervals were calculated as a hazard ratio derived from the Cox proportional hazard regression model. The assumptions of the proportional hazard model (proportional hazard, lack of interaction and linearity of continuous variables) were tested and found valid unless otherwise indicated. There was not a linear relation between parameter estimate and the variables insulin, glucose, HbA1c, and albumin. For this reason the importance of insulin, glucose, HbA1c, and albumin was studied as quartiles in multivariable models. The initial Cox model was derived from all possible confounders, excluding intermediaries and variables closely related to the variables under study. The four variables of interest were all part of the pool of candidate variables. A backward selection model was applied and variables with a p-value > 0.1 were removed from the model. The final decision to accept or reject the four variables of interest depended on analysis of the linear hypothesis that the variables representing levels of each parameter could be removed from the model. With a p-value of 0.03 this was not the case, and the quartiles remained in the model. The remaining variables were added together in the final model, which thus included the following variables: age, heart failure, wall motion index, and insulin. All tests were two-sided and a p-value of <0.05 was considered significant. All calculations were generated by the Statistical Analysis System (SAS Institute, Cary, NC, USA).
Table 1 Baseline characteristics of 494 patients in quartiles of fasting plasma insulin

<table>
<thead>
<tr>
<th>Fasting insulin (mU/l)</th>
<th>&lt;6.4 (n = 122)</th>
<th>6.4–9.3 (n = 122)</th>
<th>9.4–13.5 (n = 125)</th>
<th>&gt;13.5 (n = 125)</th>
<th>Total</th>
<th>p-value (n = 494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>70</td>
<td>70</td>
<td>66</td>
<td>72</td>
<td>69</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (47–83)</td>
<td>66 (45–85)</td>
<td>69 (48–83)</td>
<td>69 (48–83)</td>
<td>67</td>
<td>0.15</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.6 (16.8–28.6)</td>
<td>25.3 (20.2–31.0)</td>
<td>25.4 (20.5–33.2)</td>
<td>27.9 (21.9–34.6)</td>
<td>25.3 (19.3–33.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>86 (68–104)</td>
<td>90 (74–110)</td>
<td>94 (75–115)</td>
<td>100 (81–118)</td>
<td>92 (73–115)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombolytic therapy (%)</td>
<td>51</td>
<td>48</td>
<td>50</td>
<td>40</td>
<td>47</td>
<td>0.14</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>7</td>
<td>13</td>
<td>14</td>
<td>26</td>
<td>15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>13</td>
<td>20</td>
<td>15</td>
<td>26</td>
<td>19</td>
<td>0.043</td>
</tr>
<tr>
<td>History of angina pectoris (%)</td>
<td>33</td>
<td>38</td>
<td>36</td>
<td>43</td>
<td>37</td>
<td>0.13</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>15</td>
<td>14</td>
<td>30</td>
<td>26</td>
<td>21</td>
<td>0.003</td>
</tr>
<tr>
<td>Findings at day 2–5:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>35</td>
<td>45</td>
<td>52</td>
<td>58</td>
<td>47</td>
<td>0.0002</td>
</tr>
<tr>
<td>Wall Motion Index</td>
<td>1.6 (0.9–2.0)</td>
<td>1.5 (0.9–2.0)</td>
<td>1.6 (0.8–2.0)</td>
<td>1.4 (0.8–2.0)</td>
<td>1.5 (0.9–2.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak-enzyme CKB (U/l)</td>
<td>54 (14–248)</td>
<td>53 (18–235)</td>
<td>55 (13–197)</td>
<td>43 (15–198)</td>
<td>53 (15–227)</td>
<td>0.47</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>93 (68–127)</td>
<td>95 (69–142)</td>
<td>101 (72–162)</td>
<td>100 (73–179)</td>
<td>97 (69–150)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.3 (4.2–6.6)</td>
<td>5.3 (4.5–6.6)</td>
<td>5.6 (4.8–7.4)</td>
<td>5.9 (5.0–8.6)</td>
<td>5.5 (4.5–7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>4.7 (3.9–5.9)</td>
<td>4.7 (4.0–6.1)</td>
<td>4.8 (3.8–6.2)</td>
<td>4.9 (4.1–6.1)</td>
<td>4.8 (3.9–6.1)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Urinary albumin concentration (mg/l)</td>
<td>12 (0–95)</td>
<td>8.5 (0–105)</td>
<td>15.2 (2.3–235)</td>
<td>17.9 (3–408)</td>
<td>13.1 (2–210)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Continuous variables are presented as medians with 5–95 percentiles in parenthesis. BMI = Body Mass Index (kg/m²), MI = myocardial infarction, CKB = Creatinine Kinase isoenzyme B, Hba1c = Glycosylated haemoglobin.
Results

Fasting serum insulin levels

Median fasting serum insulin at day 2–5 after admission was 9.4 mU/l (5 and 95 percentiles: 4.0–24.0 mU/l). The material was divided into subgroups according to quartiles of fasting serum insulin. Baseline characteristics in quartiles of insulin concentration are shown in Table 1. The number of males, age and smoking habits were comparable in the four groups. High insulin levels were related to a high body mass index and a large abdominal circumference at admission ($p < 0.0001$). Patients in the upper quartile of insulin had a more frequent history of congestive heart failure and hypertension. The higher the insulin levels the higher the level of glucose, HbA1c and urinary albumin concentration. Kaplan–Meier estimates for subjects in quartiles of insulin are shown in Fig. 1. In a univariable Cox regression analysis, the upper quartile of insulin had an RR of 1.8 (95% CI 1.2–2.7), $p = 0.002$ compared to the lower quartile.

Fasting plasma glucose level

Median fasting plasma glucose was 5.5 mmol/l (4.5–7.7 mmol/l). Mortality rates of subjects in quartiles of fasting plasma glucose are shown in Fig. 2. In a univariable regression analysis with a default risk ratio of 1.0 for the lower quartile, there was a relative risk for the upper quartile of glucose of 1.6 (95% CI 1.2–2.1), $p = 0.001$.

Glycosylated haemoglobin levels

Median HbA1c was 4.8 (3.9–6.1). The upper normal range of the method used was 6.1%. Twenty-one subjects (4.3%) had HbA1c values above 6.1% and thereby a possible undiagnosed diabetes mellitus or impaired glucose tolerance. The calculations and following statistical analyses were therefore performed both with and without these subjects. The results were similar and the patients with HbA1c above 6.1% were not excluded from the study. Kaplan–Meier estimates for total mortality in quartiles of HbA1c are shown in Fig. 3. Default risk ratio was 1.0 for the first quartile. In a univariable analysis we found a relative risk of 1.9 (95% CI 1.3–2.9), $p = 0.001$ in the upper quartile compared to the lower quartile.
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Median urinary albumin concentration was 13.1 (2–210) mg/l. It is not possible to make a reliable stratification of the subjects into normal, microalbuminuric, or proteinuric on the basis of only one measurement of the albumin concentration. However, if microalbuminuria was defined as an albumin concentration of 20–200 mg/l, 61% were normal, 34% were microalbuminuric, and 5% were proteinuric. Kaplan–Meier estimates of total mortality in quartiles of albumin concentration are shown in Fig. 4. In a univariable regression analysis there was a risk ratio for the upper quartile of urinary albumin concentration of 1.6 (1.2–2.1), \( p = 0.02 \) compared to the lower quartile.

### Multivariable analysis

The predictive value for 6–8 year all-cause mortality of fasting insulin, glucose, HbA1c, and urinary albumin were tested adjusting for the possible confounding baseline variables. The model included age, gender, history of hypertension, heart failure, renal disease, wall motion index, insulin, glucose, HbA1c, and albumin. There was only a modest correlation between the four variables of interest, the highest between insulin and glucose. The Spearman correlation co-efficients were between 0.15 and 0.41, thus we were able to perform a multivariable analysis including all four variables of interest in the same model. Hazard ratios following backwards elimination of the non-significant variables are shown in Table 2. Of the above mentioned possible predictors, only insulin remained a significant predictor of mortality with a risk ratio of 1.54 (1.03–2.31), \( p = 0.04 \), for the upper quartile compared to the lower quartile (and a \( p \)-value of 0.03 to remove all quartiles of insulin from the model). Age, heart failure and wall motion index were the major predictors of mortality. However, due to a limited number of patients and the interrelations of the studied variables, some variables may have lost their power. Excluding the 21 patients with HbA1c above 6.1% at baseline did not change the results. Fasting glucose, HbA1c, urinary albumin concentration, gender, history of hypertension and renal disease were all non-significant predictors and therefore eliminated from the model. Excluding patients with fasting plasma glucose above 7 mmol/l yielded the same results although they failed to reach significance because of the smaller number of patients (HR = 1.4 (95% CI 0.9–2.1), \( p = 0.15 \)).

### Discussion

This study is the first to investigate the prognostic effect of serum insulin levels in patients with acute myocardial infarction. The results suggest that in univariable analysis, increased levels of fasting insulin, glucose, HbA1c, and urinary albumin concentration 2–5 days after admission for an acute myocardial infarction are associated with an increase in all-cause mortality. As in the main study, mortality was related to baseline clinical characteristics such as age, heart failure, renal function, and left ventricular systolic function, but in the present substudy the observation period was extended to 7 years. Only insulin level in the upper quartile remained significantly associated to mortality in multivariable analysis. This indicates that hyperinsulinaemia measured after a

![Fig. 4](image-url). Cumulative mortality from all causes stratified in quartiles of urinary albumin concentration (U-Alb): First: U-Alb <5.7 mg/l; Second: U-Alb 5.7–13 mg/l; Third: U-Alb 13.1–32.4 mg/l; Fourth: U-Alb >32.4 mg/l. Log Rank Test, \( p = 0.01 \).

### Table 2 Hazard ratios (HR) for total mortality

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(a)</td>
<td>1.06</td>
<td>1.03–1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.1</td>
<td>1.3–3.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Wall motion index(b)</td>
<td>1.9</td>
<td>1.1–3.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.54</td>
<td>1.03–2.31</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Relative risks and 95% CI were calculated as a hazard ratio derived from the Cox proportional hazard regression model on total mortality following backwards elimination of the non-significant variables. Insulin denotes the upper quartile of fasting plasma insulin compared to the lowest quartile. Covariates included in the initial model were age, gender, history of hypertension, heart failure, renal disease, wall motion index, and groups of insulin, glucose, HbA1c, and albumin.

\(a\) Relative risk given is per unit increase of the variable.

\(b\) Relative risk given is per unit decrease of the variable.
recent myocardial infarction independently predicts 7-year mortality in non-diabetic patients.

Although there were more patients with a history of hypertension in the hyperinsulinaemic group, history of hypertension was not significantly associated with mortality in this subgroup of patients. Neither was body mass index or abdominal circumference. With reservations for clustering with other risk factors, especially dyslipidaemia, hyperinsulinaemia was the most important prognostic feature of the insulin resistance syndrome in the present study. Lipids were not measured in this subgroup of patients screened in the TRACE study, and hyperlipidaemia or dyslipidaemia related to pre-diabetes or impaired glucose tolerance could have been an independent predictor of mortality after myocardial infarction in the present population.18 It is well known that lipid levels decrease in response to a myocardial infarction and levels measured at day 2–5 would therefore be of limited value.

Acute myocardial infarction induces a transient decline in insulin secretion and a deterioration of glucose tolerance.16 The decline in insulin secretion is induced by an increase in the activity of the sympathoadrenal system. Relatively low insulin levels should therefore follow large infarction and heart failure indicating a poor prognosis. The fact that high insulin levels predicts a poor prognosis in this study therefore suggests that fasting insulin at day 2–5 is most likely a measure of the severity of insulin resistance prior to the myocardial infarction, rather than an indirect measure of the disturbance of the glucose metabolism induced by the myocardial infarction.

In vitro studies show that insulin has both atherogenic (in supraphysiological concentrations) and antiatherogenic (in physiological concentrations) effects on the vessels.19 The latter vasodilatory action might be lost or down-regulated in the insulin resistant state, where increased insulin action in combination with hyperglycaemia leads to smooth muscle cell hypertrophy and hyperplasia, and excess synthesis of extra-cellular matrix proteins.19

Insulin resistance as well as hyperinsulinaemia is positively correlated to the degree of atherosclerosis in the coronary arteries in non-diabetic patients.20 In concordance with our results, a recent study by Stubbs and colleagues with a median follow-up time of 3 years suggested that insulin resistance at admission seems to predict subsequent cardiac death in non-diabetic patients with acute coronary syndrome,21 and measurement of admission insulin resistance index may be superior to admission plasma glucose measurements.

A recent study showed that plasma insulin 2-h post-glucose challenge was a better predictor of all cause mortality in the general population and the effect of fasting plasma insulin on mortality declined over time.22 Data on 2-h insulin post-glucose challenge were not available in this cohort of patients with acute myocardial infarction, and we did not find any evidence of the effect of insulin declining over time in this 7-year follow-up, thus we are not able to confirm the finding in this population. However, looking at the mortality curves, it appears that after 7 years the lowest and highest quartile seem closer together (Fig 1).

Type 2 diabetes is a strong risk factor for cardiovascular disease23 and mortality rates for diabetic patients with acute myocardial infarction is nearly two times higher than those in non-diabetic patients.24 Furthermore, the increased risk is associated with anti-diabetic treatment possibly reflecting the severity of metabolic disturbances.25 In the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, admission blood glucose was associated with total mortality after a mean follow-up of 3.4 years26 even though increased casual blood glucose at admission may not be a reliable measure to establish a diagnosis of diabetes.27 Fasting plasma glucose on day 2–5 mirrors both the degree of hyperglycaemia prior to the infarction and probably also the magnitude of the stress. Stress hyperglycaemia is related to in-hospital mortality in both diabetic and non-diabetic patients.28 Formation of advanced glycosylated end-products (AGE) and the activation of protein kinase C in the vessels19 may, together with hyperinsulinaemia and the other features of the metabolic syndrome,29 be working on these slightly elevated glucose levels in the precipitation of atherosclerosis and thrombosis.

Urinary albumin excretion on day 2–5 post-myocardial infarction reflects both the acute stress and the overall vascular dysfunction.6,30 Microalbuminuria is associated with widespread vascular dysfunction.31 Possibly due to an acute vascular damage, a myocardial infarction is followed by a transient increase in albuminuria that predicts in-hospital and 1-year mortality.32–34 Our results indicate that increased urinary albumin below the strip-positive level in a univariable analysis, is associated with an increased mortality rate. In a multivariable analysis however, urinary albumin was not independently associated with 7-year mortality (p = 0.15), which contrast to the study by Berton et al.33 In this study, 26% of the subjects were diabetics and urinary albumin may be of stronger predictive value after myocardial infarction in diabetic patients compared to non-diabetics. Studies on this issue are warranted.

Conclusion

We conclude, that high insulin level, age and estimates of left ventricular systolic function were independently associated with 7-year all-cause mortality following acute myocardial infarction in non-diabetic subjects. Insulin level is a valid measure of the severity of insulin resistance, and insulin level may therefore be a target for future primary and secondary interventions.

Acknowledgement

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