Prognostic value of admission glucose and glycosylated haemoglobin levels in acute coronary syndromes

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Summary

Background: Admission hyperglycaemia is associated with poorer prognosis in patients with an acute coronary syndrome (ACS). Whether hyperglycaemia is more important than prior long-term glucose metabolism, is unknown.

Aim: To investigate the prognostic value of admission glucose and HbA1c levels in patients with ACS.

Methods: We measured glucose and HbA1c at admission in 521 consecutive patients with suspected ACS. Glucose was categorized as <7.8 (n=305), 7.8–11.0 (n=138) or ≥11.1 mmol/l (n=78); HbA1c as <6.2% (n=420) or ≥6.2% (n=101). Mean follow-up was 1.6 ± 0.5 years.

Results: The diagnosis of ACS was confirmed in 332 patients (64%), leaving 189 (36%) with atypical chest pain. In ACS patients, mortality by glucose category (<7.8, 7.8–11.0 or ≥11.1 mmol) was 9%, 8% and 25%, respectively (p=0.001); mortality by HbA1c category (<6.2% vs ≥6.2%) was 10% vs. 17%, respectively (p=0.14). On multivariate analysis, glucose category was significantly associated with mortality (HR 3.0, 95%CI 1.1–8.3), but HbA1c category was not (HR 1.5, 95%CI 0.6–4.2).

Discussion: Elevated admission glucose appears more important than prior long-term abnormal glucose metabolism in predicting mortality in patients with suspected ACS.

Introduction

Diabetes is associated with a poor prognosis in patients with an acute coronary syndrome (ACS), either with or without ST-elevation (STEMI/non-STEMI).1–3 However, more acute glycometabolic disturbances may also have a negative impact on outcome. Elevated glucose levels on admission are associated with increased mortality after ACS, irrespective of diabetic status.4–8 Recent evidence has shown that chronic glucose dysregulation, as assessed by glycosylated haemoglobin (HbA1c) levels, may also be of prognostic value with regard to future cardiovascular disease.9,10 Whether HbA1c levels have the same prognostic significance as glucose levels in an emergency setting is unknown. We investigated the independent prognostic value of HbA1c levels and admission glucose in patients with ACS.

Methods

Patients

This was a single-centre, prospective follow-up study. During the 5-month study period (October...
2002 to March 2003), all patients attending the emergency department with a suspected ACS were included in this analysis.11 If patients revisited our hospital with cardiac complaints during the study period, only the first visit was recorded. Medical data from the patient’s medical record were collected in a dedicated database. Patients were included if they had a STEMI or a non-STEMI or non-specific chest pain complaints. All patients with electrocardiographic ST segment elevation on admission underwent immediate coronary angiography, and percutaneous intervention was done where indicated.

**Laboratory measurements**

Laboratory measurements were done on blood samples drawn as soon as possible after admission. HbA1c was measured using high-performance liquid affinity chromatography (HPLC) (Primus GLC 385). This method has an interassay coefficient of variation of 0.51%. Glucose was measured by a hexokinase method using a Modular PPE module device (Roche Analytics). Cholesterol was measured using an enzymatic assay.

**Definitions of clinical diagnoses**

STEMI was defined as the presence of chest pain, an electrocardiogram with ST-segment elevation of >1 mm (0.1 mV) in two or more contiguous leads, and a subsequent rise of CK values >200 U/l. Non-STEMI or unstable angina was defined as chest pain at rest, accompanied by electrocardiographic evidence of ischaemia (ST depression, ST elevation or T-wave inversion) or an elevation of cardiac troponins above threshold levels. Atypical chest pain was diagnosed as chest pain not attributable to myocardial ischaemia or other (non) cardiac causes of chest discomfort, with a normal electrocardiogram and without troponin elevation. Patients with a non-ischaemic clinical diagnosis likely to cause chest pain complaints (i.e. pneumonia or stenotic valvular disease) were excluded from the analysis. Previous CAD was defined as history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention. Diabetes was defined as the use of insulin or glucose-lowering medication on admission, or a diet for diabetes documented in medical history. Patients were categorized according to glucose level at admission (<7.8, 7.8–11.0 and ≥11.1 mmol/l), based on values reported by the American Diabetes Association for diagnosing impaired glucose tolerance and diabetes after oral glucose tolerance tests, and according to admission HbA1c (<6.2% and ≥6.2%).

**Follow-up**

Follow-up information with regard to mortality status was obtained in August 2004. All out-patients’ reports were reviewed, and general practitioners or patients were contacted by phone.

**Statistical analysis**

Statistical analysis used SPSS 12.0. Differences between group means were tested by two-tailed Student’s t-test (normal distribution) or non-parametrical tests (skewed distribution). A χ² statistic was calculated to test differences between proportions, with calculation of relative risks and 95%CIs. Fisher’s exact test was used when the expected value of cells was <5. Statistical significance was taken as p<0.05. Admission glucose was included as a continuous and as a categorized (<7.8, 7.8–11.0 and ≥11.1 mmol/l) variable. HbA1c level was also included as a continuous and categorized (<6.2% and ≥6.2%) variable. Comparison of means from continuous data between more than two patient groups was performed using one-way ANOVA analysis. Cox proportional-hazards regression models were used to estimate hazard ratios of clinical variables with regard to mortality.

**Results**

During the study period, 521 patients fulfilled the inclusion criteria. Mean age was 63 ± 13 years, 61% were male and 15% had diabetes. Of the patients with diabetes (n = 79), 52 patients (66%) took oral medication; 25 (32%) used insulin. ACS was diagnosed in 332 patients (64%); 189 (36%) had atypical chest pain. Of the patients with ACS, 237 (71%) had a STEMI and 95 (29%) had a non-STEMI. Non-STEMI was treated conservatively (45%), with PCI (38%) or with CABG (16%).

Admission glucose (8.9 ± 3.8 vs. 6.8 ± 2.2 mmol/l, p<0.001) but not HbA1c (5.9 ± 1.0% vs. 5.8 ± 0.9%, p = 0.17) was higher in patients with ACS than in those with atypical chest pain. Glucose level was <7.8 mmol/l in 154 patients (46%), 7.8–11.0 mmol/l in 113 (34%), and ≥11.1 mmol/l in 65 (20%). HbA1c was <6.2% in 266 (80%), ≥6.2% in 66 (20%). Baseline characteristics of patient groups based on glucose and HbA1c are shown in Tables 1 and 2, respectively. Admission glucose and HbA1c level were significantly correlated (Spearman 0.44, p<0.001).
Mortality

At the end of follow-up, 46 patients had died (9%), 25 due to cardiac causes.

In patients with atypical chest pain (n = 189), mortality was 4% (n = 13), with <1% (n = 1) cardiac deaths. Neither admission glucose nor HbA1c level was significantly associated with mortality in these patients.

In patients with ACS (n = 332), mortality was 12% (n = 38) with 7% (n = 24) cardiac deaths. ACS mortality by glucose level was: <7.8 mmol/l, 13 (9%); 7.8–11.0 mmol/l, 16 (25%) (p = 0.001). ACS mortality was 10% vs. 17% in patients with HbA1c <6.2% vs. ≥6.2%, respectively (p = 0.14).

Mortality was very similar in STEMI (11%) vs. non-STEMI (12%). In STEMI patients, mean admission glucose and HbA1c were no significantly different in those who died vs. those who survived (glucose 12.1 ± 6.6 vs. 9.2 ± 3.2 mmol/l, p = 0.08; HbA1c 6.3 ± 1.6% vs. 5.8 ± 0.7%, p = 0.92). In non-STEMI patients, mean admission glucose was significantly higher in those who died, but HbA1c was not (glucose 10.7 ± 4.9 vs. 7.4 ± 3.1 mmol/l, p = 0.008; HbA1c 6.8 ± 1.6 vs. 6.1 ± 1.3%, p = 0.10). Survival curves for the three patient groups by admission glucose are shown in Figure 1; those for HbA1c, in Figure 2.

Multivariate analysis

To investigate the associations between glucose level, HbA1c, and outcome with respect to baseline characteristics, we used multivariate analysis. Included variables were: age, gender, and all variables that were significantly different between glucose or HbA1c categories (diabetes, current smoking, previous coronary artery disease, cholesterol level). The patient group with the lowest glucose levels (<7.8 mmol/l) was group I. Groups II (7.8–11.0 mmol/l) and III (≥11.1 mmol/l) were compared to group I.

The independent predictors of mortality were: increased age (HR 1.7 per decade, 95%CI 1.2–2.4); previous CAD (HR 2.1, 95%CI 1.0–4.4) and admission glucose category (II vs. I, HR 1.2, 95%CI 0.5–3.0; III vs. I, HR 3.0, 95%CI 1.1–8.3; III vs. II, HR 3.3, 95%CI 1.3–8.4). HbA1c level was not significantly associated with mortality (HR 1.5, 95%CI 0.9–2.4).

<table>
<thead>
<tr>
<th>Baseline characteristics in ACS patients according to admission glucose</th>
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<tbody>
<tr>
<td>Glucose level (mmol/l)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Age ≥60 years</td>
</tr>
<tr>
<td>Mean ± SD age (years)</td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td><strong>Risk factors</strong></td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Mean ± SD cholesterol (mmol/l)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Coumadin</td>
</tr>
<tr>
<td>Beta-blocker</td>
</tr>
<tr>
<td>ACE inhibitor</td>
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<tr>
<td>Statin</td>
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<tr>
<td>Loop diuretic</td>
</tr>
<tr>
<td>Other factors</td>
</tr>
<tr>
<td>Previous CAD</td>
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<tr>
<td><strong>Type of ACS (n = 332)</strong></td>
</tr>
<tr>
<td>STEMI</td>
</tr>
<tr>
<td>Non-STEMI</td>
</tr>
<tr>
<td>Mean ± SD HbA1c (%)</td>
</tr>
<tr>
<td>HbA1c ≥6.2%</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction. *p<0.05 vs. glucose ≥7.8 mmol/l; †p<0.05 vs. glucose 7.8–11.0 mmol/l.
Table 2  Baseline characteristics in ACS patients according to HbA1c level

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>&lt;6.2</th>
<th>≥6.2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>266</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>157 (59%)</td>
<td>53 (80%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean ± SD age (years)</td>
<td>63.7 ± 12.9</td>
<td>69.0 ± 10.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Females</td>
<td>85 (32%)</td>
<td>24 (36%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Risk factors:
- Diabetes: 9 (3%) vs. 40 (61%), <0.001
- Hypertension: 89 (34%) vs. 26 (39%), 0.38
- Family history: 105 (40%) vs. 25 (38%), 0.80
- Smoking: 91 (34%) vs. 17 (26%), 0.18
- Mean ± SD cholesterol (mmol/l): 5.2 ± 1.2 vs. 5.1 ± 1.3, 0.71

Medications:
- Aspirin: 87 (33%) vs. 32 (49%), 0.02
- Coumadin: 15 (6%) vs. 7 (11%), 0.15
- Beta-blocker: 93 (35%) vs. 34 (52%), 0.02
- ACE inhibitor: 39 (15%) vs. 18 (27%), 0.02
- Statin: 61 (23%) vs. 24 (36%), 0.03
- Loop diuretic: 20 (8%) vs. 11 (17%), 0.02
- Previous CAD (%): 73 (27%) vs. 31 (47%), 0.002

Type of ACS (n = 332)
- STEMI: 195 (73%) vs. 42 (64%), 0.12
- Non-STEMI: 71 (27%) vs. 24 (36%), 0.12
- Mean ± SD glucose (mmol/l): 8.1 ± 2.8 vs. 12.6 ± 4.9, <0.001
- Glucose <7.8 mmol/l: 148 (56%) vs. 6 (9%), <0.001
- Glucose 7.8–11.0 mmol/l: 90 (34%) vs. 23 (35%), 0.88
- Glucose ≥11.1 mmol/l: 28 (11%) vs. 37 (56%), <0.001

CAD, coronary artery disease; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

**Discussion**

We investigated the association between HbA1c, glucose and outcome in patients with suspected ACS. Elevated glucose on admission was a strong and independent predictor of increased mortality, but HbA1c was not.
There were major differences in baseline characteristics according to admission glucose. Patients with higher glucose were older, more often had diabetes and were less often smokers. They more often had a final diagnosis of ACS. There were also differences in baseline characteristics according to HbA1c level. Patients with HbA1c ≥ 6.2% were older and more often had diabetes or a history of CAD. There was also a clear correlation between admission glucose and HbA1c. After adjusting for these differences in baseline characteristics, admission glucose was significantly associated with poor outcome, but HbA1c was not.

HbA1c is a convenient marker of long-term glucose regulation, which can also reveal minor glycometabolic disease, such as impaired glucose tolerance, impaired fasting glucose or the metabolic syndrome.13–15 Elevated HbA1c has been associated with increased cardiovascular risk in patients both with and without diabetes.16,17 A number of reports have shown an association between elevated admission glucose and poor outcome in patients with myocardial infarction or unstable angina.4,18 This adverse association may be independent of other clinical prognostic factors.19,20 may also apply in the setting of reperfusion therapy, and persists even after correction for HbA1c levels.8,21,22 Heart failure has also been associated with a higher admission glucose in patients with myocardial infarction.23

Although both HbA1c and admission glucose may be associated with impaired prognosis, our results indicate that increased admission glucose is more important. The less clear association between HbA1c and prognosis in our analysis could be due to a limited number of patients with a relatively short follow-up in our study. However, increased HbA1c is a marker of long-term glucose regulation, whereas elevated glucose is not only a symptom of glucose dysregulation, but also of stress and general poor health. Higher admission glucose is associated with higher Killip class, larger infarct size and lower ventricular function.21 Tenerz et al. found cortisol levels to be clearly correlated with glucose levels on admission in patients with an acute myocardial infarction.9 In contrast to our findings, no association was found between admission glucose and mortality in patients with an AMI after 5.5 years follow-up, although they did report an association between outcome and HbA1c.9 These differences may relate to length of follow-up; HbA1c may have limited predictive power for short-term outcomes in patients with ACS, but its association with long-term outcome may be stronger.

Although stress-induced hyperglycaemia can partly explain the relation between admission glucose and outcome, hyperglycaemia itself can also be harmful. The thrombotic properties of platelets are increased in a hyperglycaemic environment, and this can result in additional cardiovascular complications.24 Elevated glucose levels may also be associated with increased levels of free fatty acids (FFA).25 These FFA may increase infarct size, compromise myocardial performance during acute coronary syndromes, and reduce endothelium-derived vasodilatation in myocardial tissue, limiting myocardial reperfusion.26–28 Moreover, recent reports suggest that glucose may be an important mediator in inflammatory responses. Elevated glucose levels induce an increase in inflammatory markers in healthy people, and hyperglycaemic patients with an acute myocardial infarction have an augmented inflammatory response compared to normoglycaemic patients.29,30 Intensive glycometabolic intervention may decrease the negative effects of hyperglycaemia.7

Study limitations
Non-fasting glucose levels are influenced by diurnal variation and recent meals, but in the setting of ACS, the impact on glucose levels is not likely to be substantial. Tests to detect diabetes were not routinely done, so some cases of diabetes may have been missed. However, if the observed relation between glucose and outcome was due to undiagnosed diabetes, one would have expected a more distinct association between HbA1c and mortality. No data were available on symptom onset and time to admission.

Conclusions
Elevated admission glucose predicted mortality in our ACS patients, but HbA1c did not. Acute disturbances in glucose metabolism would seem to be of greater importance than long-term derangements of glucose metabolism, in predicting short-term outcome in ACS.

References