Clinical research
Coronary heart disease

Is admission hyperglycaemia in non-diabetic patients with acute myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance?

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Aims To investigate whether admission hyperglycaemia in non-diabetic patients with acute myocardial infarction (AMI) is a surrogate for previously undiagnosed abnormal glucose tolerance.

Methods and results Two hundred non-diabetic patients with AMI were divided into three groups: 81 patients with admission glucose $<7.8$ mmol/L (group 1), 83 patients with admission glucose $\geq 7.8$ mmol/L and $<11.1$ mmol/L (group 2), and 36 patients with admission glucose $\geq 11.1$ mmol/L (group 3). Abnormal glucose tolerance, diabetes, or impaired glucose tolerance (IGT) was diagnosed by oral glucose tolerance test (OGTT). OGTT identified diabetes in 53 patients (27%) and IGT in 78 patients (39%). When the fasting glucose criteria were applied, however, only 14 patients (7%) were diagnosed as having diabetes. The prevalence of abnormal glucose tolerance was similar among the three groups: 67% in group 1, 63% in group 2, and 69% in group 3 ($P = 0.74$). The relation of fasting glucose ($r^2 = 0.50$, $P < 0.001$) and Hb A1c ($r^2 = 0.34$, $P < 0.001$) to 2-h post-load glucose was significant, but the relation of admission glucose to 2-h post-load glucose was not significant ($r^2 = 0.02$, $P = 0.08$). Multivariable analysis showed that fasting glucose and Hb A1c were independent predictors of abnormal glucose tolerance, but admission glucose was not.

Conclusion Admission hyperglycaemia in non-diabetic patients with AMI does not represent previously undiagnosed abnormal glucose tolerance. Fasting glucose and Hb A1c, rather than admission glucose, may be useful to predict abnormal glucose tolerance. However, these parameters lacked sensitivity. OGTT should be considered in all non-diabetic patients with AMI.

Introduction

Elevation of plasma glucose is a common feature early after acute myocardial infarction (AMI). In recent years, much attention has been paid to the evidence that concomitant occurrence of hyperglycaemia in patients with AMI increases the risk of mortality. In a meta-analysis of 19 articles, Capes et al. showed that hyperglycaemia with AMI was associated with an increased risk of in-hospital mortality in patients with and without diabetes mellitus. Recent studies have reported that admission hyperglycaemia may be a more important determinant for short-term mortality after AMI than a history of diabetes, and diabetes itself does not increase short-term mortality if admission glucose is not elevated. Several studies have suggested the possible toxic action of acute increase of plasma glucose. However, it has been still discussed that admission hyperglycaemia in non-diabetic patients could simply be a marker of pre-existing, but previously undiagnosed, abnormal glucose tolerance. It has been reported that abnormal glucose tolerance, diabetes, or impaired glucose tolerance (IGT), is common in patients with AMI who have no previous diagnosis of diabetes. Some of the previous studies regarding non-diabetic patients with admission hyperglycaemia as having diabetes. It is of clinical interest whether all non-diabetic patients with admission hyperglycaemia should be treated as patients with abnormal glucose tolerance, because newly diagnosed abnormal glucose tolerance increases mortality and morbidity in patients who survived AMI. However, little is known about the association between admission hyperglycaemia and previously undiagnosed abnormal glucose tolerance. This study was undertaken to investigate whether admission hyperglycaemia could represent abnormal glucose tolerance in patients with AMI who had no previous diagnosis of diabetes.

Methods

Patients

We prospectively enrolled patients with AMI who had no previous diagnosis of diabetes mellitus. Between August 1999 and...
December 2003, 447 patients with AMI were admitted to Hiroshima City Hospital within 24 h after the onset of chest pain. We excluded 120 patients with previous diagnosis of diabetes, 12 patients without diabetes who died during hospitalization, and 10 patients without diabetes who underwent coronary bypass surgery. Among the remaining 305 patients, informed consent was obtained and oral glucose tolerance test (OGTT) was performed in 200 patients. There was no significant difference in admission glucose (8.9 ± 2.4 vs. 9.5 ± 3.2 mmol/L, P = 0.10) and baseline characteristics between the study patients and the remaining 105 patients who were not included to this study, except for shorter time to angiography in the study patients (4.1 ± 4.3 vs. 6.3 ± 6.1 h, P < 0.001).

AMI was diagnosed by chest pain consistent with ongoing myocardial ischaemia persisting longer than 30 min and concomitant electrocardiographic changes. Serum creatine kinase was measured every 3 h and peak creatine kinase value had to be more than twice the normal upper limit. This study was approved by the Ethics Committee of Hiroshima City Hospital. Informed consent was obtained from each patient.

Protocol
Plasma glucose was measured at the time of hospital admission. Patients were divided into three groups according to admission glucose:

- Group 1: patients with no or mild admission hyperglycaemia (admission glucose <7.8 mmol/L).
- Group 2: patients with moderate admission hyperglycaemia (admission glucose ≥7.8 mmol/L and <11.1 mmol/L).
- Group 3: patients with severe admission hyperglycaemia (admission glucose ≥11.1 mmol/L).

One week later, before hospital discharge, a standard OGTT with 75 g glucose was performed after overnight fasting. No patient received insulin and hypoglycaemic drugs within 72 h before OGTT. We defined abnormal glucose tolerance, diabetes, or IGT, according to the World Health Organization (WHO) criteria.21 Thus, diabetes was defined as fasting glucose >7.0 mmol/L and/or 2-h post-load glucose ≥11.1 mmol/L, IGT as fasting glucose <7.0 mmol/L and 2-h glucose of 7.8–11.0 mmol/L, and normal glucose tolerance as fasting glucose <7.0 mmol/L and 2-h glucose <7.8 mmol/L. The values of 7.8 mmol/L and 11.1 mmol/L were also used for classification of admission hyperglycaemia. One patient with IGT who had impaired fasting glucose, defined as fasting glucose of 6.1–6.9 mmol/L, was classified as IGT. The term abnormal glucose tolerance was used to describe the presence of newly diagnosed diabetes or IGT. We also assessed the prevalence of diabetes by the fasting glucose criteria suggested by American Diabetes Association (ADA), defined as fasting glucose ≥7.0 mmol/L.22 At the time of OGTT, fasting and 2-h post-load insulin, HbA1c, total cholesterol, HDL cholesterol, and triglycerides were also measured.

Statistical analysis
Categorical data are reported as proportions and continuous data as mean values with standard deviations. Variables were compared across the three groups with Cochran–Armitage test for categorical variables and the test for trend across ordered groups for continuous variables. Simple regression analyses were performed to assess the relation of admission glucose, fasting glucose, and HbA1c to 2-h post-load glucose. Nominal logistic regression analysis was performed to assess independent predictors of abnormal glucose tolerance, adjusting for baseline characteristics and variables except 2-h post-load glucose and insulin. Admission glucose, fasting glucose, fasting insulin, HbA1c, fasting lipids, age, sex, hypertension, current smoking, prior myocardial infarction, Killip class, infarct location, time to admission, and body mass index were included in the model. We used the JMP statistical package (version 5.0.1 J) and SAS statistical package (version 8.2). A significance level of 0.05 was used and two-tailed tests were applied.

Results
We enrolled 200 patients with AMI who had no previous diagnosis of diabetes. OGTT identified diabetes in 53 patients (27%), IGT in 78 patients (39%), and normal glucose tolerance in 69 patients (35%). When the fasting glucose criteria were applied, however, only 14 patients (7%) were diagnosed as having diabetes.

The mean admission glucose concentration was 8.9 ± 2.4 mmol/L. There were 81 patients with admission glucose <7.8 mmol/L (group 1), 83 patients with admission glucose 7.8–11.1 mmol/L (group 2), and 36 patients with admission glucose ≥11.1 mmol/L (group 3). Baseline characteristics and variables of the three groups are shown in Table 1. There was no significant difference in baseline characteristics and variables, except lower prevalence of prior myocardial infarction, higher Killip class, and higher HbA1c in patients with higher admission glucose levels.

Results of OGTT are shown in Figure 1. Fifteen patients (19%) in group 1, 21 patients (25%) in group 2, and 17 patients (47%) in group 3 had newly diagnosed diabetes (P-value for trend = 0.002). IGT was identified in 39 patients (48%) of group 1, 31 patients (37%) of group 2, and 8 patients (22%) of group 3 (P-value for trend = 0.008). Although diabetes was most frequent in group 3, IGT was more frequent in group 1 and group 2. There was no significant difference in the prevalence of normal glucose tolerance among the three groups: 33% in group 1, 37% in group 2, and 31% in group 3 (P-value for trend = 0.92). To assess admission glucose as a continuous variable, we also compared admission glucose between patients with normal glucose tolerance and patients with abnormal glucose tolerance. There was no significant difference in admission glucose between patients with normal glucose tolerance and patients with abnormal glucose tolerance (8.9 ± 2.4 vs. 8.9 ± 2.4 mmol/L, P = 0.93).

Figure 2 shows the relation of admission glucose, fasting glucose, and HbA1c to 2-h post-load glucose. The relation of fasting glucose (r² = 0.50, P < 0.001) and HbA1c (r² = 0.34, P < 0.001) to 2-h post-load glucose was significant. However, there was no significant relation between admission glucose and 2-h post-load glucose (r² = 0.02, P = 0.08).

Receiver operating characteristics (ROC) curves assessing the ability of baseline variables to detect newly diagnosed diabetes are shown in Figure 3. The area under the curve was 0.90 for fasting glucose (P < 0.001), 0.85 for HbA1c (P < 0.001), and 0.65 for admission glucose (P = 0.003). Figure 4 shows ROC curves assessing the ability of baseline variables to detect abnormal glucose tolerance. The area under the curve was 0.76 for fasting glucose (P < 0.001) and 0.71 for HbA1c (P < 0.001), but it was 0.50 for admission glucose (P = 0.93). Multivariable analysis showed that fasting glucose (P < 0.001) and HbA1c (P = 0.01) were independent predictors of abnormal glucose tolerance, but admission glucose was not (Table 2).
Admission hyperglycaemia in patients with AMI

It has been reported that abnormal glucose tolerance is common among patients with AMI who have no previous diagnosis of diabetes. Norhammar et al.\textsuperscript{13} performed OGTT in non-diabetic patients with AMI at hospital discharge and showed that 31 and 35\% of the patients were diagnosed with diabetes and IGT, respectively. Recently, the Euro Heart Survey on diabetes and the heart reported that abnormal glucose tolerance was not addressed in these previous studies.

Two decades before, Oswald and Yudkin\textsuperscript{24} performed OGTT at 3 months after AMI in 110 patients with no previous diagnosis of diabetes and reported that Hb\textsubscript{A1c} was a better marker for newly diagnosed diabetes than admission hyperglycaemia. The prevalence of newly diagnosed diabetes in the entire study patients was, however, only 8\%. Recently, Tenerz et al.\textsuperscript{25} assessed 285 patients with AMI and showed that 5 (60\%) of 12 non-diabetic patients with admission glucose $\geq$11 mmol/L had diabetes. However, they used the fasting glucose criteria and newly diagnosed diabetes was identified in only 4\% of patients without a history of diabetes. In the current study, the fasting glucose criteria missed diabetes in 39 of 53 patients (74\%) in whom diabetes was diagnosed by OGTT.

By using OGTT, we investigated the association between admission glucose levels and the prevalence of abnormal glucose tolerance. Two-thirds of patients with AMI and no previous diagnosis of diabetes were diagnosed as having newly diagnosed abnormal glucose tolerance (diabetes or IGT). Of note, there was no significant difference in the prevalence of abnormal glucose tolerance among the three groups. One-thirds of patients with severe admission hyperglycaemia had normal glucose tolerance. Although severe admission hyperglycaemia was associated with higher prevalence of diabetes, more than half of patients with severe admission hyperglycaemia did not have diabetes. On the other hand, nearly quarter of patients without severe admission hyperglycaemia had diabetes. These findings suggest that, although abnormal glucose tolerance is common in non-diabetic patients with AMI, admission hyperglycaemia does not represent abnormal glucose tolerance.

It has been well demonstrated that patients with admission hyperglycaemia are associated with increased risk of mortality after AMI. This association has been observed not only in diabetic patients but also patients who had no previous diagnosis of diabetes. Recent experimental and clinical studies suggested that rapid elevation of plasma glucose itself increases infarct size. Hyperglycaemia activates blood coagulation, aggregates inflammation,

### Table 1 Baseline characteristics and variables in three groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 81)</th>
<th>Group 2 (n = 83)</th>
<th>Group 3 (n = 36)</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.2 ± 12.5</td>
<td>62.7 ± 11.6</td>
<td>64.9 ± 12.6</td>
<td>0.31</td>
</tr>
<tr>
<td>Men, n(%)</td>
<td>72 (89)</td>
<td>69 (86)</td>
<td>28 (78)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>27 (33)</td>
<td>36 (43)</td>
<td>17 (47)</td>
<td>0.11</td>
</tr>
<tr>
<td>Current smoking, n(%)</td>
<td>45 (56)</td>
<td>44 (53)</td>
<td>19 (53)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior myocardial infarction, n(%)</td>
<td>14 (17)</td>
<td>9 (11)</td>
<td>1 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Killip class $\geq$ 2, n(%)</td>
<td>2 (2)</td>
<td>16 (19)</td>
<td>4 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anterior location, n(%)</td>
<td>42 (52)</td>
<td>36 (43)</td>
<td>17 (47)</td>
<td>0.48</td>
</tr>
<tr>
<td>Time to admission (h)</td>
<td>4.4 ± 4.8</td>
<td>3.8 ± 3.7</td>
<td>4.1 ± 4.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>23.7 ± 3.1</td>
<td>23.8 ± 3.5</td>
<td>23.7 ± 3.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission glucose (mmol/L)</td>
<td>6.9 ± 0.6</td>
<td>9.2 ± 1.0</td>
<td>13.0 ± 2.0</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.3 ± 0.8</td>
<td>5.4 ± 1.0</td>
<td>5.5 ± 0.9</td>
<td>0.09</td>
</tr>
<tr>
<td>2-h glucose (mmol/L)</td>
<td>9.2 ± 3.2</td>
<td>9.4 ± 3.3</td>
<td>10.7 ± 4.2</td>
<td>0.06</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>5.2 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>5.5 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting insulin (IU/L)</td>
<td>9.8 ± 6.4</td>
<td>8.3 ± 4.6</td>
<td>8.4 ± 4.5</td>
<td>0.10</td>
</tr>
<tr>
<td>2-h insulin (IU/L)</td>
<td>92.6 ± 81.2</td>
<td>73.3 ± 54.8</td>
<td>68.0 ± 34.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.06 ± 0.94</td>
<td>4.86 ± 0.69</td>
<td>5.02 ± 1.01</td>
<td>0.47</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.98 ± 0.31</td>
<td>0.97 ± 0.25</td>
<td>0.97 ± 0.26</td>
<td>0.75</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.66 ± 0.81</td>
<td>1.54 ± 0.76</td>
<td>1.70 ± 0.80</td>
<td>0.90</td>
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<tr>
<td>HOMA-IR</td>
<td>2.38 ± 1.89</td>
<td>2.08 ± 1.47</td>
<td>2.13 ± 1.38</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Discussion

Figure 1 Prevalence of diabetes, IGT, and normal glucose tolerance. Although diabetes was most frequent in group 3, IGT was more frequent in group 1 and group 2. There was no significant difference in the prevalence of abnormal glucose tolerance (diabetes or IGT) among the three groups. Group 1, patients with admission glucose $<7.8$ mmol/L; Group 2, patients with admission glucose $\geq 7.8$ mmol/L and $<11.1$ mmol/L; Group 3, patients with admission glucose $\geq 11.1$ mmol/L.
attenuates endothelium function, and abolishes ischaemic preconditioning.\textsuperscript{8–11}

Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study demonstrated that intensive insulin treatment to attain normoglycaemia reduced mortality after AMI in patients with admission hyperglycaemia.\textsuperscript{19} Recently, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)—Estudios Cardiologicas Latin America (ELCA) trial reported that glucose–insulin–potassium therapy had neutral effect on mortality.\textsuperscript{26} However, the infusion rate of the solution was fixed and glucose level after randomization was significantly higher in the infusion patients than control patients. In a meta-analysis of insulin therapy for critically ill hospitalized patients, insulin therapy decreased short-term mortality when the aim of therapy was glucose control.\textsuperscript{27} No benefit was seen when insulin was administered without regard to glucose levels. Intensive insulin infusion to achieve normoglycaemia thus improves outcome of patients with AMI and hyperglycaemia. In the community practice, however, elevated glucose is rarely treated in patients with AMI and that fewer hyperglycaemic patients without diabetes receive insulin during hospitalization than diabetic patients with similar glucose levels.\textsuperscript{28}

Although diabetes predicted morbidity and mortality after AMI in the thrombolysis era, recent progress in treatment of AMI has improved short-term outcome of diabetic patients. Percutaneous coronary intervention (PCI) is more effective than thrombolytic therapy among diabetic patients with AMI and is similarly successful in diabetic and non-diabetic patients.\textsuperscript{29} Brener et al.\textsuperscript{30}, reviewing data from the international Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery (GUSTO) IIb and ReoPro and Primary PTCA Organization and Randomized Trial (PAPPORT), have shown that diabetes was not associated with 30-day mortality after primary PCI. Recently, we have reported that admission hyperglycaemia, but not diabetes, was a predictor for in-hospital mortality after AMI in the PCI era.\textsuperscript{7} These findings suggest that admission hyperglycaemia and abnormal glucose tolerance should be considered as two distinct disease status. However, several investigators discussed that hyperglycaemia in non-diabetic patients could represent pre-existing, but previously undiagnosed, abnormal glucose tolerance. To assess this issue, we focused on the relation between admission hyperglycaemia and the prevalence of abnormal glucose tolerance in non-diabetic patients with AMI. This study showed that admission hyperglycaemia was not a surrogate for previously undiagnosed abnormal glucose tolerance.

\textbf{Figure 2} Simple regression analysis assessing relation of admission glucose (left), fasting glucose (mid), and HbA\textsubscript{1c} (right) to 2-h post-load glucose. Although the relation of fasting glucose ($P < 0.001$) and HbA\textsubscript{1c} ($P < 0.001$) to 2-h post-load glucose was significant, there was no significant relation between admission glucose and 2-h post-load glucose ($P = 0.08$).

\textbf{Figure 3} ROC curves of admission glucose (left), fasting glucose (mid), and HbA\textsubscript{1c} (right) to detect diabetes. The area under the curve was 0.65 for admission glucose ($P = 0.003$), 0.90 for fasting glucose ($P < 0.001$), and 0.85 for HbA\textsubscript{1c} ($P < 0.001$).
Although recent studies have reported that diabetes may not be a predictor for short-term outcome after AMI in the PCI era, abnormal glucose tolerance is still an important determinant of long-term outcome. Several studies have suggested that not only diabetes but also IGT has an increased risk of morbidity and mortality from cardiovascular disease. The Funagata Diabetes Study, a cohort study from Japan, reported that survival rate from cardiovascular disease in subjects with IGT was comparable with that of diabetics, and significantly lower than in those with normal glucose tolerance or impaired fasting glucose.31 Recently, Bartnik et al.20 have demonstrated that abnormal glucose tolerance is a strong risk factor for future cardiovascular events after AMI. The difference in the incidence of cardiovascular events between patients with newly diagnosed diabetes and patients with IGT was negligible. Taking into account the considerably high prevalence of abnormal glucose tolerance among patients with AMI and no previous diagnosis of diabetes, OGTT could be routinely considered for the risk stratification. However, OGTT is seldom done in coronary care units. More simple and rapid measures are preferable in routine clinical practice. Several studies have reported that fasting glucose and HbA1c were good measures to predict abnormal glucose tolerance.14,24,32 We also showed that fasting glucose and HbA1c, but not admission glucose, were associated with 2-h postload glucose and were independent predictors of abnormal glucose tolerance. Rapidity of fasting glucose and HbA1c may be useful to predict abnormal glucose tolerance of non-diabetic patients who survived AMI regardless of the presence or absence of admission hyperglycaemia. However, these parameters lacked sensitivity to predict abnormal glucose tolerance. Fasting glucose criteria could predict diabetes in only one-quarter of the patients who were diagnosed as having diabetes by OGTT. OGTT should be considered in all patients with AMI and no previous diagnosis of diabetes.

Study limitation

This study diagnosed abnormal glucose tolerance on a single OGTT that was performed 1 week after AMI. During the phase of acute stress, the inflammation response to the infarct may influence the result of OGTT. Tenerz et al.25 reported that, of 76 patients with fasting glucose ≥5.6 mmol/L at fifth day after AMI, 51 (67%) patients had...
fasting glucose <5.6 mmol/L at follow-up of 2–3 months. To investigate whether OGTT in the early phase of AMI could identify established abnormal glucose metabolism, Norhammar et al.\textsuperscript{13} performed OGTT in 181 non-diabetic patients before hospital discharge (day 4 or 5) and 3 months later. They showed that the prevalence of abnormal glucose tolerance was comparable between the two study periods, suggesting that abnormal glucose tolerance could be identified by OGTT in the early phase of AMI. Another issue of our study is that abnormal glucose tolerance was identified on a single OGTT. Several studies have demonstrated intra-individual variability of OGTT. In the sub-analysis of the aforementioned study by Norhammar et al.,\textsuperscript{13} the intra-individual tracking of OGTT from discharge to follow-up was fairly poor, although an OGTT before discharge from hospital after AMI provided a reliable estimate of abnormal glucose tolerance classified at 3 months.\textsuperscript{33} Brohail et al.\textsuperscript{34} recently reported the high variability in results of OGTT even when it was repeated within 2 weeks. For more accurate estimate of abnormal glucose tolerance, repeated OGTT should be advocated.

Conclusion

Two-thirds of patients with AMI who had no previous diagnosis of diabetes had abnormal glucose tolerance by OGTT 1 week after AMI, regardless of admission glucose levels. Admission hyperglycaemia in non-diabetic patients with AMI did not represent previously undiagnosed abnormal glucose tolerance. Fasting glucose and HbA1c may be more useful than admission glucose to predict abnormal glucose tolerance in non-diabetic patients who survived AMI for 7 days. However, sensitivity of these parameters was not high enough to predict abnormal glucose tolerance. OGTT should be considered in all non-diabetic patients with AMI.

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References


