Can Admission and Fasting Glucose reliably identify Undiagnosed Diabetes in Patients with Acute Coronary Syndrome?

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Objective: Our objectives were: (1) to determine the prevalence of previously undiagnosed abnormal glucose tolerance i.e. diabetes and impaired glucose tolerance (IGT) in patients with acute coronary syndrome, and (2) to assess the utility of admission and fasting glucose in identifying diabetes in these patients.

Research Design and Methods: Glycaemic status was characterised based on admission plasma glucose (APG), fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) in 140 patients admitted to hospital with acute coronary syndrome who were not known to have diabetes (mean age 67.3 ± 13.4 years; males 79%). OGTTs were performed on days 5-7 following admission.

Results: The prevalence of diabetes and IGT was 27% and 39% respectively according to OGTT criteria. Receiver operating characteristics (ROC) curves showed that the area under the curve (AUC) for diagnosing diabetes was 0.83 (p<0.001) for FPG, 0.79 (P<.001) for admission glucose and 0.84 (p<0.001) for fasting and admission glucose applied in combination. A fasting glucose cutoff ≥ 5.6 mmol/L (100 mg/dl) and/or admission glucose ≥ 7.8 mmol/L (140 mg/dl) yielded a sensitivity of 89.5% and a positive predictive value of 43.6% for detecting diabetes.

Conclusions: A high prevalence of abnormal glucose tolerance was seen in patients with acute coronary syndrome. The combination of FPG ≥5.6 mmol/L (100 mg/dl) and/or APG ≥ 7.8 mmol/L (140 mg/dl) was highly sensitive for identifying diabetes. Although weakly specific, this simple algorithm could offer a practical initial screening tool at the acute setting in the high risk acute coronary syndrome population.
Diabetes mellitus is associated with increased cardiovascular risk. Individuals with diabetes have a greater mortality from acute myocardial infarction (AMI) than non-diabetic individuals [1]. Following an acute coronary event hyperglycaemia has been shown to be a predictor of immediate and long-term cardiovascular mortality [2]. Although the prevalence of diabetes mellitus has continued to rise, many patients with diabetes remain undiagnosed. In recent years several studies have reported an increased prevalence of prior undiagnosed abnormal glucose tolerance i.e. impaired glucose tolerance (IGT) and diabetes in patients with AMI [3-6]. Furthermore, such newly-diagnosed abnormalities of glucose metabolism have been shown to be associated with an excess long-term cardiovascular mortality [7]. Thus, patients with acute coronary syndrome present an opportunity for targeted screening for diabetes and institution of effective management strategies aimed at improving cardiovascular outcome.

The optimal strategy for identifying individuals with diabetes in the setting of an acute coronary syndrome is however unclear. Although the oral glucose tolerance test (OGTT) is considered the gold standard for the diagnosis of diabetes, its utility is hampered by its cost, time consuming protocol, and overall inconvenience when compared to simple fasting or admission glucose measurements. Accordingly, clinicians in practice often adopt the more pragmatic approach of characterising glycaemic status based on admission and fasting glucose. The Joint British Societies’ 2005 clinical guidelines on prevention of cardiovascular disease recommend that a fasting glucose can be done as an alternative to the OGTT in patients who have suffered an acute cardiovascular event [8]. However, there is increasing evidence to suggest that fasting glucose alone will miss a substantial proportion of patients with diabetes following an acute myocardial infarction [4]. Studies specifically addressing this issue in the setting of the full spectrum of the acute coronary syndrome are limited. Likewise, the diagnostic utility of admission glucose in patients with coronary events has received little attention even though hyperglycaemia in this setting could potentially represent pre-existing undiagnosed diabetes mellitus.

Thus, it remains unresolved if an OGTT is mandatory following an acute coronary syndrome or if admission and fasting glucose could effectively identify patients with diabetes or in the least stratify individuals who will merit an OGTT. Our objective in this study was first to clarify the prevalence of unrecognised abnormal glucose tolerance in our own population of patients with acute coronary syndrome in South Wales, United Kingdom. Secondly, we analysed the performance of fasting and admission glucose, applied individually or in combination, as markers of previously undiagnosed diabetes in patients with acute coronary syndrome.

RESEARCH DESIGN AND METHODS

Patients: We studied 140 patients who were admitted consecutively to our coronary care unit with a diagnosis of acute coronary syndrome. We excluded patients with previously known diabetes or IGT. Clinical and demographic data were obtained for each patient including blood pressure, lipid profile and body mass index. A casual blood glucose sample was taken on the day of admission, usually on arrival to the coronary care or emergency unit. Where more than one admission glucose level was available, the highest reading was selected for analysis. A standardised 75 gram OGTT was performed prior to discharge, usually between days 5 and 7. This was performed in the morning, after a 12-hour overnight fast according to the World Health Organisation (WHO) protocol [9].
**Laboratory analysis:** Blood samples were separated within 30 minutes of collection, centrifuged (2000g x 5 minutes) at 4°C and plasma glucose was assayed by an automated glucose oxidase method. Total cholesterol and triglycerides were also analysed in fasting samples. Cardiac troponin T was measured on admission and at least 12 hours after the primary clinical event.

**Definitions:** Glycaemic status was classified based on the 2 hour post load (2-hPG) glucose values of the OGTT according to the WHO 1998 definitions [9] as: normal glucose tolerance (NGT) < 7.8 mmol/l (140 mg/dl); IGT 7.8-11.0 mmol/l (140-200 mg/dl) and diabetes ≥11.1 mmol/l (200 mg/dl). Patients were also stratified according to FPG based on the American Diabetes Association (ADA) 2004 criteria [10]. The cutoff limits for FPG were: (1) <5.6 mmol/l (100 mg/dl) (NGT), (2) 5.6-6.9 mmol/l (100-125 mg/dl) (IFG), and (3) ≥ 7.0 mmol/l (126 mg/dl) (diabetes). Admission glucose was stratified into three groups: (1) <7.8 mmol/l (140 mg/dl), (2) 7.8-11.0 mmol/l (140-200 mg/dl) and (3) ≥ 11.1 mmol/l (200 mg/dl).

The diagnosis of AMI was based on the joint recommendations by the European Society of Cardiology and American College of Cardiology [11]. AMI was diagnosed if there was a typical rise and gradual fall in the levels of cardiac troponins with at least one of the following features: typical ischaemic cardiac chest pain and compatible electrocardiograph changes of myocardial infarction or ischaemia. Unstable angina was diagnosed if patients had cardiac chest pain either at rest, of new-onset, or of an accelerating nature, accompanied by electrocardiograph changes of ischaemia and negative cardiac troponins [12].

**Statistical analysis:** Values are presented as means ± SD except where otherwise stated. All statistical analysis was performed using SPSS for windows, version 12.0. Characteristics of patients in the different glycaemic groups were compared using the chi-squared test for categorical data or the one way analysis of variance (ANOVA) for continuous data with the Tukey’s post-hoc procedure applied for multiple group comparisons. The relationship between different measurements of plasma glucose was examined with the Pearson’s correlation coefficients. We determined the sensitivity, specificity and positive predictive values for fasting and admission glucose. Sensitivity was calculated as the percentage of patients with diabetes who had a fasting or admission plasma glucose above the designated cutoff point. Specificity was the percentage of patients without diabetes who had a fasting or admission glucose below the chosen cutoff point. We generated receiver operating characteristics (ROC) curves to determine the accuracy of fasting and admission glucose as indicators of diabetes. An area under the curve was calculated for each indicator and the optimal cutoff point for the detection of diabetes was estimated from the ROC. The level of statistical significance at which the null hypothesis was rejected was chosen as 0.05.

**RESULTS**

**Patient characteristics:** The baseline characteristics of the patients according to the OGTT status are shown in table 1. There were no significant differences in age, gender and ethnic distribution between the various categories of glucose tolerance. The prevalence of undiagnosed IGT and DM was higher in patients with AMI than in patients with unstable angina. BMI, blood pressure, total cholesterol and triglyceride levels were not statistically significantly different between the three different glycaemic categories. FPG levels differed between all three groups while admission glucose was higher in diabetic patients than in the other groups (table 1).
Prevalence of abnormal glucose tolerance: The prevalence of diabetes and IGT based on the OGTT were 27% and 39% respectively. Of the patients with diabetes on the OGTT, 14 (37%) had a fasting glucose above 7.0 mmol/L (126 mg/dl) while 6 (16%) had admission glucose >11.1 mmol/L (200 mg/dl). Figure 1 shows the prevalence of diabetes at various cutoff points for fasting and admission glucose.

Performance of admission and fasting plasma glucose: The sensitivities, specificities and positive predictive values (PPV) for diagnosing diabetes with fasting and admission glucose are shown in table 2. FPG was more sensitive but less specific than admission glucose in detecting diabetes. The combination of both criteria led to improved sensitivity but suffered from poor specificity and positive predictive value (table 2). Using the dual fasting and admission glucose cutoff points of FPG ≥ 5.6 (100 mg/dl) and/or APG ≥ 7.8 mmol/L (140 mg/dl) as thresholds for performing an OGTT would have yielded a sensitivity of 89.5% and would have reduced the amount of OGTTs undertaken to 52% of patients.

The area under the ROC curves (AUC) for diagnosing diabetes was 0.83 (p<0.001) for fasting plasma glucose, 0.79 (P<.001) for admission glucose and 0.84 (p<0.001) for fasting and admission glucose applied in combination. The diagnostic performance of fasting and admission glucose measurements did not differ when patients were stratified according to cardiac diagnosis. The AUC was similar in patients with AMI and unstable angina (UA) for each of the diagnostic indices. For FPG, the AUC was 0.834 and 0.823 in AMI and UA patients respectively while the AUC for APG was 0.794 and 0.746 respectively. The AUC for the combined FPG and APG was 0.851 in AMI patients and 0.804 in UA patients. The optimal cutoff point for diagnosing diabetes with fasting glucose was 5.8 mmol/L (104.4 mg/dl). This is the FPG value with the best sensitivity and specificity for identifying diabetes in this setup. At this cutoff the sensitivity and specificity of FPG in detecting diabetes was 69.2% and 77.2% respectively. The optimal cutoff point for identifying diabetes with admission glucose was 7.7 mmol/L (138.6 mg/dl); this cutoff point was associated with sensitivity of 65.8% and specificity of 82.4%.

We determined the relationship between 2-hour post-load glucose and admission and fasting glucose using the Pearson’s correlation coefficients. The fasting glucose showed a better correlation to 2-hour plasma glucose (r=0.56; P<0.0001) than the admission glucose (r=0.38; P<0.0001).

CONCLUSIONS
We determined the prevalence of hitherto undiagnosed glycaemic abnormalities in patients presenting with acute coronary syndrome in our institution. Two-thirds of patients had abnormal glucose tolerance on OGTT, comprising diabetes (27%) and IGT (39%). The high prevalence of glycaemic abnormalities in our United Kingdom sample is consistent with reports from elsewhere. Norhammar and colleagues observed that 35% of Swedish patients with AMI had undiagnosed IGT while 31% had diabetes [3]. Their findings were subsequently confirmed in a large multi-centre European survey which found a prevalence of 36% for IGT, and 22% for diabetes in 923 patients with acute coronary artery disease and no previous dysglycaemia [4]. High rates of newly-detected glycaemic abnormalities have similarly been reported in other populations with acute coronary syndrome [5, 6].

Admission or fasting glucose alone underestimated the prevalence of diabetes in our study. This is in keeping with the experience of others who have shown that glycaemic status in the acute coronary syndrome may not be accurately defined by
fasting [4, 5, 13] or admission glucose [14]. Application of the diabetes cutoff points for fasting and random glucose would have missed the majority of diabetic patients. However, lower cutoff values for fasting and admission glucose were associated with better sensitivity. Using the IFG cutoff of 5.6 mmol/L (100 mg/dl) as a threshold for performing OGTTs yielded acceptable sensitivity and would have reduced the proportion of OGTTs required to 46%. The optimal FPG threshold of 5.8 mmol/L (104.4 mg/dl) would have further reduced the amount of required OGTTs but was not sufficiently sensitive for screening purposes. Combining the IFG threshold with an admission glucose cutoff of 7.8 mmol/L (140 mg/dl) offered the best sensitivity for detecting diabetes, missing only 10% of diabetic patients but requiring OGTTs to be performed in 52% of acute coronary syndrome patients. Thus, fasting and admission glucose proved useful as early markers of diabetes in our patients with acute coronary syndrome, including patients with AMI as well as those with unstable angina.

The increased frequency of undiagnosed diabetes and IGT observed in our patients is significant in the light of evidence showing that newly-diagnosed abnormal glucose tolerance in patients with acute coronary syndrome is a strong predictor of future cardiovascular mortality [7]. In the Funagata diabetes study in Japan, IGT was found to be a risk factor for cardiovascular mortality [15]. In addition, IGT appears to be an intermediate step in the development of diabetes. In a study of 1342 subjects in a Dutch population the cumulative incidence of diabetes after a mean follow-up period of 6.4 years was 64.5% in patients with IGT compared to 4.5% for those with normal glucose tolerance at baseline [16]. More importantly, it appears that this progression can be effectively delayed by the implementation of pharmacological and non-pharmacological measures like dietary adjustments and increased physical activity. In 3234 individuals with elevated but non-diabetic fasting and post-load glucose levels, lifestyle modification and treatment with metformin were individually more effective than placebo in reducing the incidence of diabetes [17].

It therefore seems prudent to identify patients with glycaemic abnormalities at the earliest possible opportunity and initiate appropriate management of their cardio-metabolic risks. The OGTT remains the gold standard for early detection of glycaemic abnormalities but continues to be underutilised in clinical practice. In the Euro Heart Survey which involved over 4000 participants in 25 European countries, an OGTT was not performed in over 50% of cases of stable and acute coronary heart disease [13]. A reluctance to perform OGTTs may reflect prevailing local policies as well as the individual preferences of clinicians in acute care settings who may opt for more practical algorithms based on fasting and random glucose. Our results indicate that fasting or admission glucose alone will underestimate the prevalence of diabetes but may be useful in selecting patients for an OGTT thereby limiting the amount of glucose tolerance tests undertaken. However, using fasting or random glucose thresholds for undertaking OGTTs would still require a considerable percentage of glucose tolerance tests and will inevitably miss a fraction of patients with diabetes and IGT.

One limitation of our study is that OGTTs were performed on a single occasion during hospital admission. It could be argued that such tests were influenced by acute stress. However, a recent study by the European Heart Survey group showed that OGTTs done in hospital within 4-5 days after an acute coronary syndrome correlated well with glycaemic status at 3 and at 12 months [18]. At present there appears to be no
consensus on the timing of OGTTs after acute coronary syndrome; in clinical studies this has ranged from 3-7 days post coronary event [4-6, 14]. Studies are required to clarify the optimal performance conditions for glucose tolerance testing following acute coronary syndrome. A pragmatic approach would be to re-evaluate glycaemic status in an outpatient setting at least two months after discharge when the effects of acute stress would have subsided. The feasibility of a two step protocol in which further testing in the outpatient setting is undertaken in patients with elevated admission fasting (≥5.6 mmol/L; 100 mg/dl) or random glucose (≥7.8 mmol/L; 140 mg/dl) deserves further evaluation.

In conclusion we observed a high prevalence of abnormal glucose tolerance in our patients with acute coronary syndrome. Fasting and admission glucose applied in combination was highly sensitive in identifying patients with diabetes. These simple measurements are readily available in the acute setting and could form a useful initial screening tool in this patient population with high rates of undiagnosed diabetes.
REFERENCES
myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance? *Eur Heart J* 27:2413-2419, 2006


Table 1: Clinical and laboratory characteristics of patients classified according to OGTT.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>OGTT classification</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>NGT n=48 (34%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IGT n=54 (39%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM n=38 (27%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.7 ± 14.1</td>
<td>67.6 ± 13.7</td>
</tr>
<tr>
<td>Males; (%)</td>
<td>81.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Ethnicity; (%)</td>
<td>94.0</td>
<td>92.0</td>
</tr>
<tr>
<td>Cardiac diagnosis; (%)</td>
<td>29.0</td>
<td>57.0</td>
</tr>
<tr>
<td>AMI</td>
<td>71.0</td>
<td>43.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 2.9</td>
<td>28.2 ± 3.2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134 ± 22.5</td>
<td>134 ± 15.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82 ± 15.7</td>
<td>77 ± 10.1</td>
</tr>
<tr>
<td>Laboratory variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.4 ± 0.8</td>
<td>4.2 ± 0.8</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.4 ± 0.7</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/l) (range)</td>
<td>6.6 ± 1.6</td>
<td>6.9 ± 1.6</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l) (range)</td>
<td>5.1 ± 0.5</td>
<td>5.6 ± 0.6</td>
</tr>
</tbody>
</table>

*Includes patients of south Asian and Afro Caribbean ethnicity.
†DM vs NGT, IGT vs NGT; ‡DM vs IGT, DM vs NGT; § DM vs IGT, DM vs NGT, IGT vs NGT.
**Table 2:** Performance of fasting plasma glucose (FPG) and admission plasma glucose (APG) in the diagnosis of diabetes in patients with acute coronary syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG $\geq$ 5.6 mmol/L</td>
<td>48%</td>
<td>81.6</td>
<td>64.7</td>
<td>46.3</td>
</tr>
<tr>
<td>APG $\geq$ 7.8 mmol/L</td>
<td>30%</td>
<td>65.8</td>
<td>83.3</td>
<td>59.5</td>
</tr>
<tr>
<td>FPG $\geq$ 5.6 or APG $&gt; 7.8$ mmol/L</td>
<td>52%</td>
<td>89.5</td>
<td>56.9</td>
<td>43.6</td>
</tr>
</tbody>
</table>
**Figure 1:** Prevalence of diabetes (according to OGTT) at various cutoff points for fasting and admission plasma glucose.