Can Admission and Fasting Glucose Reliably Identify Undiagnosed Diabetes in Patients With Acute Coronary Syndrome?

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OBJECTIVE — Our objectives were 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 to assess the utility of admission and fasting glucose in identifying diabetes in these patients.

RESEARCH DESIGN AND METHODS — Glycemic status was characterized on the basis of admission plasma glucose (APG), fasting plasma glucose (FPG), and an oral glucose tolerance test (OGTT) in 140 patients admitted to the hospital with acute coronary syndrome, who were not known to have diabetes (mean ± SD age 67.3 ± 13.4 years; 79% men). OGTTs were performed on days 5–7 after admission.

RESULTS — The prevalences of diabetes and IGT were 27 and 39%, respectively, according to OGTT criteria. Receiver operating characteristic curves showed that the area under the curve for diagnosing diabetes was 0.83 ($P < 0.001$) for FPG, 0.79 ($P < 0.001$) for APG, and 0.84 ($P < 0.001$) for FPG and APG applied in combination. A FPG cutoff ≥5.6 mmol/l (100 mg/dl) and/or APG ≥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 population with acute coronary syndrome.

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Diabetes is associated with increased cardiovascular risk. Individuals with diabetes have a greater mortality from acute myocardial infarction (AMI) than nondiabetic individuals (1). After an acute coronary event, hyperglycemia has been shown to be a predictor of immediate and long-term cardiovascular mortality (2). Although the prevalence of diabetes has continued to rise, diabetes remains undiagnosed in many patients. 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 to improve cardiovascular outcome.

The optimal strategy for identifying individuals with diabetes in the setting of an acute coronary syndrome is unclear, however. 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 compared with simple fasting or admission glucose measurements. Accordingly, clinicians in practice often adopt the more pragmatic approach of characterizing glycemic status on the basis of admission and fasting glucose values. The Joint British Societies' 2005 clinical guidelines on prevention of cardiovascular disease recommended that a fasting glucose measurement can be done as an alternative to an OGTT in patients who have had an acute cardiovascular event (8). However, there is increasing evidence to suggest that use of fasting glucose measurements alone will miss a substantial proportion of patients with diabetes after an AMI (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 measurements in patients with coronary events has received little attention even though hyperglycemia in this setting could potentially represent preexisting undiagnosed diabetes.

Thus, it remains unresolved whether an OGTT is mandatory after an acute coronary syndrome or whether admission and fasting glucose could effectively identify patients with diabetes or at the least stratify individuals who will merit an OGTT. Our objective in this study was first to clarify the prevalence of unrecognized abnormal glucose tolerance in our own population of patients with acute coronary syndrome in South Wales, U.K. Second, we analyzed the performance of fasting and admission glucose measurements, applied individually or in combination, as markers of previously undiagnosed diabetes in patients with acute coronary syndrome.

RESEARCH DESIGN AND METHODS

— We studied 140 patients who were admitted consecutively to our coronary care unit with a diagnosis of

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Table 1—*Clinical and laboratory characteristics of patients classified according to an OGTT*

Clinical characteristics	OGTT classification			*P*
	NGT	IGT	Diabetes	
n (%)	48 (34)	54 (39)	38 (27)	
Age (years)	65.7 ± 14.1	67.6 ± 13.7	69.0 ± 13.4	0.5
Sex (% male)	81.0	80.0	76.0	0.8
Ethnicity (%)				0.9
White	94.0	92.0	92.0	
Other*	6.0	8.0	8.0	
Cardiac diagnosis (%)				0.002†
AMI	29.0	57.0	63.0	
Unstable angina	71.0	43.0	37.0	
BMI (kg/m^2)	26.8 ± 2.9	28.2 ± 3.2	27.3 ± 3.2	0.08
Systolic blood pressure (mmHg)	134 ± 22.5	134 ± 15.4	135 ± 19.0	0.86
Diastolic blood pressure (mmHg)	82 ± 15.7	77 ± 10.1	83 ± 10.7	0.09
Laboratory variables				
Cholesterol (mmol/l)	4.4 ± 0.8	4.2 ± 0.8	4.6 ± 1.1	0.66
Triglyceride (mmol/l)	1.4 ± 0.7	1.5 ± 0.5	1.7 ± 0.9	0.58
APG (mmol/l)	6.6 ± 1.6 (4.2–13.4)	6.9 ± 1.6 (3.4–13.3)	9.3 ± 3.5 (5.2–19.7)	<0.001‡
Fasting plasma glucose (mmol/l)	5.1 ± 0.5 (4.0–6.8)	5.6 ± 0.6 (4.2–6.9)	6.8 ± 1.4 (4.7–10)	<0.001§

Data are *n* (%), means ± SD, or means ± SD (range). *Includes patients of south Asian and Afro-Caribbean ethnicity. †Diabetes vs. NGT; IGT vs. NGT. ‡Diabetes vs. IGT; diabetes vs. NGT. §Diabetes vs. IGT; diabetes vs. NGT; IGT vs. NGT.

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 BMI. A casual blood glucose sample was taken on the day of admission, usually on arrival to the coronary care or emergency unit. When more than one admission glucose level was available, the highest reading was selected for analysis. A standardized 75-g OGTT was performed before discharge, usually between days 5 and 7. This was performed in the morning, after a 12-h overnight fast according to the World Health Organization protocol (9).

Laboratory analysis

Blood samples were separated within 30 min of collection and centrifuged (2000*g* for 5 min) at 4°C, and plasma glucose was assayed by an automated glucose oxidase method. Total cholesterol and triglycerides were also analyzed in fasting samples. Cardiac troponin T was measured on admission and at least 12 h after the primary clinical event.

Definitions

Glycemic status was classified on the basis of the 2-h postload (2-h plasma glucose) glucose values of the OGTT according to the World Health Organization 1998 definitions (9) as follows: 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 fasting plasma glucose (FPG) on the basis of the American Diabetes Association 2004 criteria (10). The cutoff limits for FPG were <5.6 mmol/l (100 mg/dl) for NGT, 5.6–6.9 mmol/l (100–125 mg/dl) for impaired fasting glucose (IFG), and ≥ 7.0 mmol/l (126 mg/dl) for diabetes. Admission plasma glucose (APG) was stratified into three groups: <7.8 mmol/l (140 mg/dl), 7.8–11.0 mmol/l (140–200 mg/dl), and ≥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 ischemic cardiac chest pain and compatible electrocardiograph changes of myocardial infarction or ischemia. 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 ischemia and negative results for 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; SPSS, Chicago, IL). Characteristics of patients in the different glycemic groups were compared using the χ^2 test for categorical data or ANOVA for continuous data with Tukey's post hoc procedure applied for multiple group comparisons. The relationship between different measurements of plasma glucose was examined with Pearson's correlation coefficients. We determined the sensitivity, specificity, and positive predictive values (PPVs) for fasting and admission glucose. Sensitivity was calculated as the percentage of patients with diabetes who had a FPG or APG value greater than the designated cutoff point. Specificity was the percentage of patients without diabetes who had FPG or APG values below the chosen cutoff point. We generated receiver operating characteristic (ROC) curves to determine the accuracy of FPG and APG values as indicators of diabetes. An area under the ROC curve (AUC) 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 — The baseline characteristics of the patients according to OGTT status are shown in Table 1. There were no significant differences in age, sex, and ethnic distribution between the various categories of glucose tolerance. The prevalence of undiagnosed IGT and diabetes was higher in patients with AMI than in

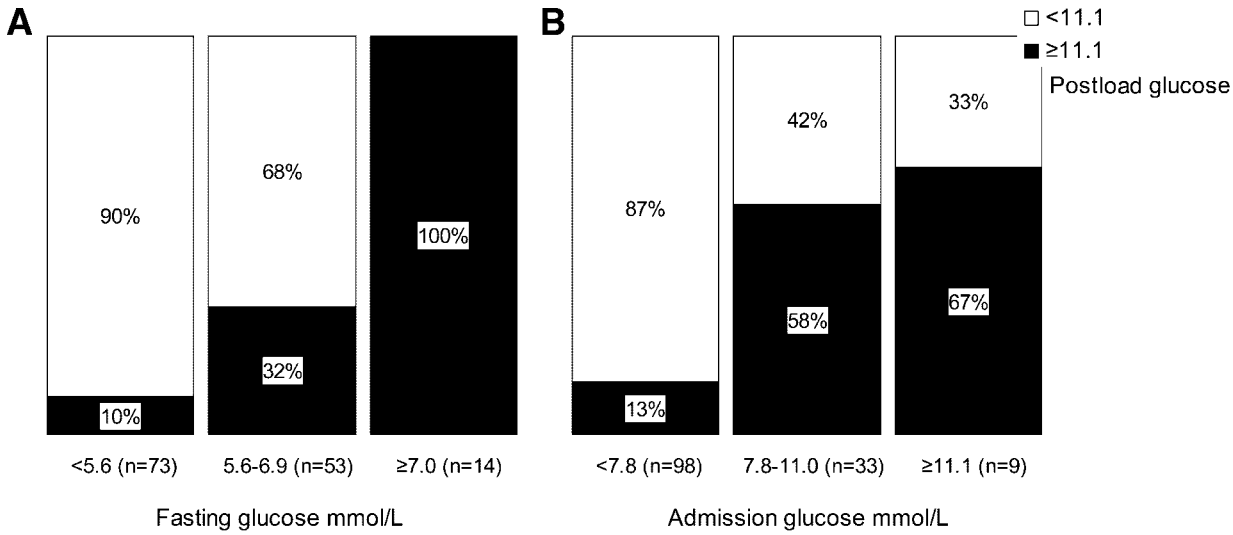

Figure 1—*Prevalence of diabetes (according to an OGTT) at various cutoff points for FPG (A) and APG (B).*

patients with unstable angina. BMI, blood pressure, total cholesterol, and triglyceride levels were not statistically significantly different between the three different glycemic categories. FPG levels differed between all three groups, whereas the APG level was higher in diabetic patients than in the other groups (Table 1).

Prevalence of abnormal glucose tolerance

The prevalences of diabetes and IGT on the basis of the OGTT were 27 and 39%, respectively. Of the patients with diabetes according to the OGTT, 14 (37%) had FPG >7.0 mmol/l (126 mg/dl), whereas 6 (16%) had APG >11.1 mmol/l (200 mg/dl). Figure 1 shows the prevalence of diabetes at various cutoff points for FPG and APG.

Performance of APG and FPG measurements

The sensitivities, specificities, and PPVs for diagnosing diabetes with FPG and APG are shown in Table 2. FPG was more sensitive but less specific than APG in detecting diabetes. The combination of both criteria led to improved sensitivity but had poor specificity and PPV (Table 2). Using the dual FPG and APG cutoff points of FPG ≥5.6 mmol/l (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 number of OGTTs performed to 52% of patients.

The AUCs for diagnosing diabetes were 0.83 ($P < 0.001$) for FPG, 0.79 ($P < 0.001$) for APG, and 0.84 ($P < 0.001$) for FPG and APG applied in combination. The diagnostic performance of FPG and APG measurements did not differ when patients were stratified according to cardiac diagnosis. The AUC was similar in patients with AMI and unstable angina for each of the diagnostic indexes. For FPG, the AUCs were 0.834 and 0.823 in patients with AMI and unstable angina, respectively, whereas the AUCs for APG were 0.794 and 0.746, respectively. The AUCs for combined FPG and APG were 0.851 in patients with AMIs and 0.804 in patients with unstable angina. The optimal cutoff point for diagnosing diabetes with FPG 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 were 69.2 and 77.2%, respectively. The optimal cutoff point for identifying diabetes with APG was 7.7mmol/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-h postload glucose and admission and FPG using the Pearson's correlation coefficients. FPG showed a better correlation to 2-h plasma glucose ($r = 0.56$; $P < 0.0001$) than APG ($r = 0.38$; $P < 0.0001$).

Table 2—*Performance of FPG and APG in the diagnosis of diabetes in patients with acute coronary syndrome*

	Prevalence	Sensitivity	Specificity	PPV
FPG ≥5.6 mmol/l	48	81.6	64.7	46.3
APG ≥7.8 mmol/l	30	65.8	83.3	59.5
FPG ≥5.6 or APG ≥7.8 mmol/l	52	89.5	56.9	43.6

Data are percent.

CONCLUSIONS — We determined the prevalence of hitherto undiagnosed glycemic abnormalities in patients presenting with acute coronary syndrome in our institution. Two-thirds of patients had abnormal glucose tolerance on an OGTT, comprising diabetes (27%) and IGT (39%). The high prevalence of glycemic abnormalities in our U.K. sample is consistent with reports from elsewhere. Norhammar et al. (3) observed that 35% of Swedish patients with AMI had undiagnosed IGT, whereas 31% had diabetes. Their findings were subsequently confirmed in a large multicenter European survey, which showed a prevalence of 36% for IGT and 22% for diabetes in 923 patients with acute coronary artery disease and no previous dysglycemia (4). High rates of newly detected glycemic abnormalities have similarly been reported in other populations with acute coronary syndrome (5,6).

APG or FPG measurements alone underestimated the prevalence of diabetes in our study. This finding is in keeping with the experience of others who have shown that glycemic status in the acute coronary

syndrome may not be accurately defined by FPG (4,5,13) or APG (14). Application of the diabetes cutoff points for FPG and random glucose measurements would have missed the majority of diabetic patients. However, lower cutoff values for FPG and APG measurements 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 number of required OGTTs but was not sufficiently sensitive for screening purposes. Combining the IFG threshold with an APG 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 patients with acute coronary syndrome. Thus, FPG and APG 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 1,342 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 with 4.5% for those with NGT at baseline (16). More importantly, it appears that this progression can be effectively delayed by the implementation of pharmacological and nonpharmacological measures such as dietary adjustments and increased physical activity. In 3,234 individuals with elevated but nondiabetic fasting and postload glucose levels, lifestyle modification and treatment with metformin were individually more effective than placebo in reducing the incidence of diabetes (17).

Therefore, it seems prudent to identify patients with glycemic abnormalities at the earliest possible opportunity and initiate appropriate management of their cardiometabolic risks. The OGTT remains the gold standard for early detection of glycemic abnormalities but continues to be underused in clinical practice. In the Euro Heart Survey, which involved >4,000 participants in 25 European countries, an OGTT was not performed in >50% of patients with 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 on the basis of FPG and random glucose values. Our results indicate that FPG or APG 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 performed. However, using FPG or random glucose thresholds for performance of OGTTs would still require a considerable percentage of OGTTs and would 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 the hospital within 4–5 days after an acute coronary syndrome correlated well with glycemic 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 to 7 days after a coronary event (4–6,14). Studies are required to clarify the optimal performance conditions for glucose tolerance testing after an acute coronary syndrome. A pragmatic approach would be to reevaluate glycemic status in an outpatient setting at least 2 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 performed in patients with elevated admission fasting (≥5.6 mmol/l; 100 mg/dl) or random glucose (≥7.8 mmol/l; 140 mg/dl) concentrations deserves further evaluation.

In summary, we observed a high prevalence of abnormal glucose tolerance in our patients with acute coronary syndrome. The combination of FPG and APG measurements 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.

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