Fasting Glucose Is an Important Independent Risk Factor for 30-Day Mortality in Patients With Acute Myocardial Infarction
A Prospective Study

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Background—Stress hyperglycemia in patients with acute myocardial infarction has been associated with increased mortality. Most studies looked at the relationship between admission glucose (AG) and outcome; limited information is available about the clinical significance of fasting glucose (FG).

Methods and Results—We prospectively studied the relationship between FG and 30-day mortality in 735 nondiabetic patients with acute myocardial infarction. FG (≥8-hour fast within 24 hours of admission) and AG were measured in each patient. At 30 days, 9 deaths (2%) occurred in patients with normal FG, and 11 (10%), 14 (13%), and 31 (29%) deaths occurred in the first, second, and third tertiles of elevated FG, respectively. Compared with normal FG (<110 mg/dL), the adjusted OR for 30-day mortality progressively increased with higher tertiles of elevated FG (first tertile, 4.6; 95% CI, 1.7 to 12.7; P = 0.003; second tertile, 6.4; 95% CI, 2.5 to 16.6; P < 0.0001; third tertile, 11.5; 95% CI, 4.7 to 20.0; P < 0.0001). Compared with patients categorized as having normal AG (<140 mg/d), the adjusted ORs for tertiles of elevated AG were as follows: first tertile, 1.4 (95% CI, 0.5 to 3.8; P = 0.54); second tertile, 3.0 (95% CI, 1.3 to 7.0; P = 0.01); and third tertile, 4.4 (95% CI, 2.0 to 9.7; P < 0.0001). Compared with patients with normal FG and AG, the adjusted ORs for 30-day mortality were 0.71 (95% CI, 0.15 to 3.4; P = 0.67) in patients with elevated AG and normal FG, 3.4 (95% CI, 1.1 to 10.4; P = 0.03) for patients with normal AG glucose and elevated FG, and 9.6 (95% CI, 3.5 to 26.0; P < 0.0001) for patients with both elevated FG and AG. Comparing nested models showed that including AG failed to improve the prediction of the model based on FG (χ² = 5.4, 3 df, P = 0.15). In contrast, the addition of FG classes to the model based on AG improved model prediction (χ² = 22.4, 3 df, P < 0.0001).

Conclusions—There is a graded relation between elevated FG and AG and 30-day mortality in patients with acute myocardial infarction. FG is superior to AG in the assessment of short-term risk. (Circulation. 2005;111:754-760.)

Key Words: glucose ▪ myocardial infarction ▪ prognosis ▪ stress

The finding of abnormally elevated blood glucose, common among patients with acute myocardial infarction, is often referred to as stress hyperglycemia. Several studies have shown that raised blood glucose concentrations on admission are associated with increased mortality and congestive heart failure. Most previous reports studied the relationship between admission glucose (AG) level and outcome, limited information is available about the clinical significance of fasting glucose (FG) in acute myocardial infarction. Furthermore, the relative risk associated with fasting hyperglycemia was not adjusted for other important factors that affect outcome. In addition, the ability of fasting hyperglycemia to predict mortality was evaluated with dichotomous groupings, eg, those above and below an arbitrary cut point, rather than through a study of its predictive value over the entire range of its possible values. Finally, the relative prognostic information provided by FG and AG in patients with acute myocardial infarction has not been evaluated.

In the present study, we prospectively evaluated the predictive value of stress hyperglycemia for 30-day mortality in nondiabetic patients with acute myocardial infarction. The prognostic importance of both FG and AG was considered and compared.

Methods

Patients
The study included all patients presenting to the intensive coronary care unit of Rambam Medical Center with acute myocardial infarc-
tion between July 2001 and January 2004. The investigational review committee on human research approved the study protocol, and patients gave informed consent.

Myocardial infarction was diagnosed on the basis of the European Society of Cardiology and American College of Cardiology criteria. Exclusion criteria were admission at >24 hours from symptom onset, known inflammatory disease, and surgery or trauma within the previous month. Qualifying patients received thrombolytic therapy (tissue plasminogen activator or streptokinase) or underwent primary coronary angioplasty according to the discretion of the attending cardiologist.

Plasma Glucose Measurements
The first blood sample for plasma glucose measurement was taken in all patients on admission. A second sample was obtained after an overnight fast of ≥8 hours within 24 hours of admission. Intravenous glucose solutions were not allowed, but adrenergic agents were used if clinically indicated. Plasma glucose was enzymatically determined with the glucose oxidase method using an AutoAnalyzer (Hitachi Inc).

Study End Points and Definitions
Patients who had a clinical diagnosis of diabetes before enrollment in the study were classified as having known diabetes. Patients were classified as having diabetes on the basis of history, regardless of duration of disease, or need for antidiabetic agents. The diagnosis was established if the patient had been informed of the diagnosis by a physician before the admission or was taking oral antihyperglycemic agents, taking insulin, or receiving diet therapy. Glycohemoglobin on admission was not used because it is not recommended for the diagnosis of diabetes by recent guidelines.14,15

Classification of normal FG and AG levels in patients who had not been diagnosed with diabetes was made prospectively according to the criteria of the American Diabetes Association14 and the 1999 report of the World Health Organization.16 On the basis of fasting plasma glucose, patients were classified as having normal FG using a cutoff level of <110 mg/dL (6.1 mmol/L).14,16 Patients with elevated FG levels (FG ≥110 mg/dL) were divided into tertiles of elevated FG. While the study was in progress, the American Diabetes Association lowered the threshold for normal glucose to <100 mg/dL (5.6 mmol/L). Therefore, additional analyses were made with this new threshold.

On the basis of admission (random) plasma glucose, patients were classified as having normal levels using a cutoff level of <140 mg/dL (7.8 mmol/L).14,16 Patients with elevated AG levels (AG ≥140 mg/dL) were divided into tertiles of elevated AG.

The primary end point of the study was all-cause mortality within 30 days. Secondary end points included the combined end point of death and heart failure developing ≥24 hours after admission. Development of heart failure was defined as rules over more than half of the lung field and evidence of pulmonary congestion on a chest radiograph. Patients were followed up throughout their hospital stay. After hospital discharge, clinical end-point information was acquired by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital records for major clinical events if the patient had been rehospitalized.

Statistical Analysis
Continuous variables are presented as either means (±SD) or medians (with interquartile ranges); categorical variables, as numbers and percentages. The baseline characteristics of groups categorized by FG level were compared by use of ANOVA for continuous variables and by the χ² statistic for noncontinuous variables. Correlations among continuous variables were assessed with Spearman’s rank correlation coefficient.

FG and AG were modeled with indicator variables divided into normal (<110 mg/dL for FG, <140 mg/dL for AG)13 and tertiles of elevated FG and AG. The ORs and 95% CIs compared with normal (<100 mg/dL)14 resulted in 129 patients (17.6%) initially classified as having normal FG being reclassified as having elevated FG. With this cutoff value for normal FG, the adjusted ORs for 30-day mortality in tertiles of elevated FG were calculated for patients in the first, second, and third tertiles of elevated FG and AG.

Event-free survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate logistic regression models were used to calculate ORs and 95% CIs for various glucose categories after adjustment for the following baseline clinical characteristics: age, gender, previous infarction, heart rate and systolic blood pressure on admission, Killip class on admission, history of hypertension, presence of ST-elevation infarction, presence of anterior infarction, peak creatine kinase, and reperfusion therapy with either thrombolytic agents or primary angioplasty. Variables found to show marginal association with 30-day mortality in the univariate analysis (P<0.20) were used in the multivariate model.

Nested models were compared by use of χ² likelihood ratio tests to determine whether logistic regression models that included categories of FG and AG provided a significantly better fit than did logistic regression models limited to FG and vice versa. In addition, comparison of nonnested models including either FG or AG was performed by calculating Akaike’s information criterion, followed by Akaike weights, which is an estimate of the probability that a given model is the best model of those studied.17,18

Receiver-operating characteristics analysis was used to assess the ability of various levels of FG and AG to predict 30-day mortality. The receiver-operating characteristics curve indicates the probability of a true-positive result as a function of the probability of a false-positive result for all possible threshold values.19 Differences were considered statistically significant at the 2-sided P<0.05 level. Statistical analyses were performed with SPSS statistical software, version 11.5.

Results
Subject Sample and Demographics
Between July 2001 and January 2004, a total of 735 nondiabetic patients who presented with acute myocardial infarction were enrolled. Data were also collected from 310 patients with known diabetes who were admitted during the study period. The median FG and AG levels of patients without prior diagnosis of diabetes were 115 mg/dL (interquartile range, 97 to 149 mg/dL) and 147 mg/dL (interquartile range, 117 to 218 mg/dL), respectively. The median length of time between AG and FG measurements was 14.7 hours.

The clinical characteristics of nondiabetic patients according to categories of FG (normal FG, tertiles of elevated FG, and diabetes) are shown in Table 1. Elevated levels of FG were associated with older age, male gender, and history of hypertension. Patients presenting with elevated FG were more likely to have ST-segment elevation or anterior infarction and had higher heart rates and Killip class on admission. Use of aspirin, β-blockers, ACE inhibitors, and statins was less frequent in patients with elevated FG. They were more likely to be treated with primary angioplasty.

Relation of Stress Hyperglycemia to 30-Day Mortality
A total of 65 deaths (8.8%) occurred at 30 days. Kaplan-Meier survival curves (Figure 1) and unadjusted logistic regression analysis showed a striking increase in the risk of 30-day mortality with increasing tertiles of elevated FG (Table 2). After adjustment for other important covariates, elevated FG remained a strong independent predictor of 30-day mortality (Table 2).

Using the new American Diabetes Association criteria for normal FG (<100 mg/dL)14 resulted in 129 patients (17.6%) initially classified as having normal FG being reclassified as having elevated FG. With this cutoff value for normal FG, the adjusted ORs for 30-day mortality in tertiles of elevated FG...
compared with normal FG were as follows: first tertile, 2.3 (95% CI, 0.63 to 8.7; \( P < 0.021 \)); second tertile, 7.3 (95% CI, 2.3 to 22.8; \( P < 0.0006 \)); and third tertile, 11.7 (95% CI, 4.0 to 34.7; \( P < 0.0001 \)).

Similar relationships existed when patients were classified according to AG levels. The adjusted OR for excess 30-day mortality progressively increased with higher tertiles of elevated AG compared with normal FG (Table 3). Because the selection of a “normal” value for FG and AG in the setting of acute myocardial infarction is likely to be somewhat arbitrary,14,15 receiver-operating characteristics curves of the ability of various glucose levels to predict 30-day mortality were plotted. The threshold levels of FG and AG that maximized the combined sensitivity and specificity for the prediction of 30-day mortality were close to the cutoff levels that were prospectively chosen (114 mg/dL for FG, 151 mg/dL for AG).

### TABLE 1. Baseline Clinical Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal FG (n=409)</th>
<th>First, 100–121 (n=109)</th>
<th>Second, 122–138 (n=109)</th>
<th>Third, 139 (n=108)</th>
<th>Diabetes (n=310)</th>
<th>( P ) for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±13</td>
<td>61±12</td>
<td>62±14</td>
<td>64±13</td>
<td>65±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>347 (85)</td>
<td>88 (81)</td>
<td>81 (74)</td>
<td>84 (78)</td>
<td>213 (69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous infarct, n (%)</td>
<td>81 (20)</td>
<td>22 (20)</td>
<td>17 (16)</td>
<td>28 (26)</td>
<td>94 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>275 (67)</td>
<td>63 (58)</td>
<td>69 (63)</td>
<td>63 (58)</td>
<td>93 (30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>180 (44)</td>
<td>56 (51)</td>
<td>55 (51)</td>
<td>62 (57)</td>
<td>208 (67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP at admission, mm Hg</td>
<td>128±23</td>
<td>132±31</td>
<td>128±30</td>
<td>127±32</td>
<td>133±32</td>
<td>0.36</td>
</tr>
<tr>
<td>Heart rate at admission, bpm</td>
<td>74±17</td>
<td>79±17</td>
<td>78±17</td>
<td>85±25</td>
<td>84±19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class at admission</td>
<td>1.2±0.5</td>
<td>1.5±0.9</td>
<td>1.4±0.9</td>
<td>2.0±1.2</td>
<td>1.7±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ST-elevation infarction, n (%)</td>
<td>285 (70)</td>
<td>82 (75)</td>
<td>90 (83)</td>
<td>87 (81)</td>
<td>202 (65)</td>
<td>0.45</td>
</tr>
<tr>
<td>Anterior infarction, n (%)</td>
<td>170 (42)</td>
<td>51 (47)</td>
<td>49 (45)</td>
<td>60 (56)</td>
<td>143 (46)</td>
<td>0.1</td>
</tr>
<tr>
<td>Peak CK, IU/L</td>
<td>934 (470–1945)</td>
<td>1311 (802–2684)</td>
<td>1715 (769–2797)</td>
<td>2353 (1005–4672)</td>
<td>1869 (773–3202)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Initial medical therapies, n (%)

- Aspirin: 403 (99) 106 (96) 105 (98) 99 (92) 292 (94) 0.001
- \( \beta \)-Blockers: 362 (89) 100 (90) 83 (78) 87 (81) 266 (86) 0.09
- ACE inhibitors/A-II receptor blockers: 331 (81) 87 (80) 86 (79) 76 (70) 270 (87) 0.15
- Statins: 260 (64) 59 (54) 62 (57) 52 (49) 188 (61) 0.28

Reperfusion therapy, n (%)

- Thrombolysis: 115 (28) 31 (28) 24 (22) 26 (24) 54 (17) 0.001
- Primary angioplasty: 87 (21) 26 (24) 34 (31) 34 (32) 55 (18) 0.63

BP indicates blood pressure; CK, creatine kinase; and Ang II, angiotensin II. Values are expressed as mean±SD or median (interquartile range) as appropriate. Trends for categorical variables were calculated with the Cochran-Armitage trend test.

*To convert from mg/dL to mmol/L, multiply plasma glucose values by 0.0555.
Comparison of FG and AG in Predicting 30-Day Mortality

There was a moderate correlation between FG and AG (Spearman’s ρ, 0.40; P<0.0001). We found only a modest relationship between the FG and AG sets of criteria for stress hyperglycemia. Among 735 patients with no history of diabetes, 294 patients (40%) were classified as having both normal FG and AG, 115 (16%) as having elevated AG and normal FG, and 184 (25%) as having elevated FG and AG.

Compared with patients with normal FG and AG, the adjusted ORs for 30-day mortality were 0.71 in patients with elevated AG and normal FG (95% CI, 0.15 to 3.4; P=0.46), 3.4 for patients with normal AG and elevated FG (95% CI, 1.1 to 10.4; P=0.03), and 9.6 for patients with both elevated FG and AG (95% CI, 3.5 to 26.0; P<0.0001) (Figure 2).

Log-likelihood ratio tests were used to compare the fit of predictive models that were based on categories of FG (Table 2) combined with categories of AG (Table 3) and vice versa. Comparing nested models showed that including the AG classes did not significantly improve the prediction of the model based on FG and other risk factors for 30-day mortality (χ²=5.4, 3 df, P=0.15) or for 30-day mortality and heart failure (χ²=4.6, 3 df, P=0.20). In contrast, the addition of FG classes to the model based on AG and other risk factors significantly improved the prediction of the model for both 30-day mortality (χ²=22.4, 3 df, P<0.0001) and 30-day mortality and heart failure (χ²=22.3, 3 df, P=0.0001).

Overall, AG concentrations were not independently related to mortality after adjustment for FG concentrations. Similar results were obtained when nonnested models were compared. The model containing FG classes yielded the best Akaike’s information criterion and demonstrated a 99% probability of representing the best model.

Effect of Diabetes

Of the 310 patients with known diabetes, 42 were receiving insulin treatment with or without oral agents (14%), 184 were receiving oral agents (59%), and 84 were on diet therapy (27%). The median FG and AG levels of patients with known diabetes were significantly higher than those of patients without diabetes (FG: Mann-Whitney P<0.0001; difference in medians, 54 mg/dL; and AG: Mann-Whitney P<0.0001; difference in medians, 111 mg/dL). There was a significant

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**TABLE 2. Unadjusted and Adjusted Logistic Regression for 30-Day Mortality According to Categories of FG Levels**

<table>
<thead>
<tr>
<th>FG, mg/dL†</th>
<th>n</th>
<th>Events (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>P for Trend</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;110)</td>
<td>409</td>
<td>9 (2.2)</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, first tertile (110–121)</td>
<td>109</td>
<td>11 (10.0)</td>
<td>5.0 (2.0–12.4)</td>
<td>0.001</td>
<td>4.6 (1.7–12.7)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, second tertile (122–138)</td>
<td>109</td>
<td>14 (12.8)</td>
<td>6.6 (2.8–15.6)</td>
<td>&lt;0.0001</td>
<td>6.4 (2.5–16.6)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, third tertile (≥139)</td>
<td>108</td>
<td>31 (28.7)</td>
<td>17.9 (8.2–39.1)</td>
<td>&lt;0.0001</td>
<td>11.5 (4.7–20.0)</td>
<td>&lt;0.0001</td>
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</table>

Death and heart failure

<table>
<thead>
<tr>
<th>FG, mg/dL†</th>
<th>n</th>
<th>Events (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>P for Trend</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;110)</td>
<td>409</td>
<td>23 (5.6)</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, first tertile (110–121)</td>
<td>109</td>
<td>17 (15.6)</td>
<td>3.1 (1.6–6.0)</td>
<td>0.0009</td>
<td>2.8 (1.4–5.9)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, second tertile (122–138)</td>
<td>109</td>
<td>21 (19.3)</td>
<td>4.0 (2.1–7.6)</td>
<td>&lt;0.0001</td>
<td>3.9 (1.9–7.8)</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated, third tertile (≥139)</td>
<td>108</td>
<td>37 (31.5)</td>
<td>8.7 (4.9–15.6)</td>
<td>&lt;0.0001</td>
<td>5.6 (2.8–10.9)</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

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*The final model was adjusted for age, gender, history of hypertension, presence of anterior infarction and ST-elevation infarction, Killip class, heart rate and blood pressure on admission, and use of reperfusion therapy.

†To convert from mg/dL to mmol/L, multiply plasma glucose values by 0.0555.
interaction between diabetes and both FG (P = 0.007) and AG (P = 0.02) because the relationship between increasing levels of AG or FG and 30-day mortality was much weaker among patients with diabetes.

To evaluate whether previously undiagnosed diabetes could account in part for the relationship between FG and outcome in nondiabetic patients, we performed a multivariate logistic regression analysis using the combined data from patients with and without previously diagnosed diabetes. In this model, patients were divided into 4 groups. Patients without a previous diagnosis of diabetes were classified according to the American Diabetes Association14 as having normal FG, impaired FG, or FG in the diabetes range (a category that by definition includes all patients with undiagnosed diabetes); the fourth group included patients with known diabetes. Compared with patients with normal FG, the adjusted OR for 30-day mortality was much higher in patients without previous diagnosis of diabetes and FG in the diabetes range (≥126 mg/dL [7.0 mmol/L]) compared with patients with known diabetes (Table 4).

**Discussion**

In the present study, we prospectively evaluated the prognostic value of fasting hyperglycemia in nondiabetic patients presenting with acute myocardial infarction. Compared with patients who maintain normal FG levels, those who develop elevated FG have more adverse baseline clinical characteristics. However, fasting hyperglycemia remains a strong and independent predictor of 30-day mortality after adjustment for established clinical predictors of adverse outcome among patients with acute myocardial infarction,20,21 with a striking increase in short-term mortality with small increases of FG above normal levels. Furthermore, FG concentrations are better predictors of mortality than AG.

**TABLE 4. Unadjusted and Adjusted Logistic Regression for 30-Day Mortality According to the Level of FG and Presence of Known Diabetes**

<table>
<thead>
<tr>
<th>End Point</th>
<th>n</th>
<th>Events (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FG (≤110 mg/dL)†</td>
<td>409</td>
<td>9 (2.2)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Impaired FG (110–125 mg/dL)</td>
<td>145</td>
<td>14 (9.7)</td>
<td>4.8 (2.0–11.2)</td>
<td>0.0004</td>
<td>4.0 (1.5–10.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>FG in the diabetes range (≥126 mg/dL)</td>
<td>181</td>
<td>42 (23.2)</td>
<td>13.4 (6.4–28.3)</td>
<td>&lt;0.0001</td>
<td>10.2 (4.4–23.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previously known diabetes</td>
<td>310</td>
<td>35 (11.3)</td>
<td>5.7 (2.7–11.0)</td>
<td>&lt;0.0001</td>
<td>2.4 (1.03–5.5)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Death and heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FG (≤110 mg/dL)†</td>
<td>409</td>
<td>24 (5.9)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Impaired FG (110–125 mg/dL)</td>
<td>145</td>
<td>22 (15.2)</td>
<td>3.0 (1.6–5.6)</td>
<td>0.0005</td>
<td>2.6 (1.3–5.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>FG in the diabetes range (≥126 mg/dL)</td>
<td>181</td>
<td>56 (30.9)</td>
<td>6.9 (4.1–11.8)</td>
<td>&lt;0.0001</td>
<td>5.8 (3.3–10.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previously known diabetes</td>
<td>310</td>
<td>48 (15.5)</td>
<td>3.1 (1.8–5.2)</td>
<td>&lt;0.0001</td>
<td>1.6 (0.9–2.9)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Adjusted for the covariates listed in Table 2.
†To convert from mg/dL to mmol/L, multiply plasma glucose values by 0.0555.
In an overview of previous reports using data from 1856 patients, Capes et al calculated a pooled unadjusted relative risk of 3.9 (95% CI, 2.9 to 5.4) for in-hospital mortality in patients without diabetes who had stress hyperglycemia, defined heterogeneously as elevated FG or AG. These authors noted varying definitions of stress hyperglycemia among studies, ranging from 119 mg/dL (6.6 mmol/L) to 200 mg/dL (11.1 mmol/L) for random glucose and from 110 mg/dL (6.1 mmol/L) to 140 mg/dL (7.8 mmol/L) for FG. This resulted in a marked difference in the proportion of nondiabetic patients defined as having stress hyperglycemia (3% to 71%).

There is paucity of data on the potential use of FG for risk stratification in patients with acute myocardial infarction, because most studies used glucose concentration on admission. Ravid et al and Soler et al reported a higher unadjusted prevalence of in-hospital mortality among nondiabetic patients with elevated FG. Using a cutoff value of 144 mg/dL (8 mmol/L) for fasting hyperglycemia, O’Sullivan et al reported a relative risk of 2.8 (95% CI, 0.9 to 8.3) for in-hospital mortality after adjustment for age. Recently, Zeller et al studied the prognostic value of impaired FG (110 to 126 mg/dL) determined at days 4 and 5 after admission. Impaired FG was an independent predictive factor for cardiogenic shock (adjusted OR, 2.8; 95% CI, 1.08 to 7.49; P=0.005) but failed to be an independent predictor of in-hospital death.

Our study confirms the observations of smaller studies and extends them in several important ways. First, stress hyperglycemia remains a strong and independent predictor of 30-day mortality after adjustment for established clinical predictors of adverse outcome among patients with acute myocardial infarction. Second, in the present study, we avoided the use of a dichotomous definition of stress hyperglycemia. Our results indicate that the risk for 30-day mortality among nondiabetic subjects with FG within the normal range is very low. Within the range of elevated FG levels, the risk increases dramatically across tertiles of elevated FG. A substantial increased risk for short-term mortality was observed at any level of abnormal FG and well below the diabetic threshold. Third, although elevations of both FG and AG concentrations were significant independent predictors of mortality when used alone, our results indicate that elevated FG concentrations are better predictors of mortality than AG. In patients with normal FG, elevated AG did not incur an increased risk of death compared with patients with normal FG and AG concentrations. In contrast, patients with elevated FG and normal AG had a 3-fold increase in mortality. Furthermore, when categories (tertiles) of elevated FG are used for risk stratification, elevated AG did not contribute significantly to the prediction of mortality, whereas adding FG categories to models containing AG provided additional prognostic information. The superiority of FG over random glucose levels in predicting outcome probably results from factors such as differences in the amount of caloric intake and time since the last meal.

Several hypotheses (which are not mutually exclusive) have been put forward to explain the relation between stress hyperglycemia and poor outcome. Stress hyperglycemia may be a marker of extensive myocardial damage, reflecting a surge of stress hormones such as catecholamines and cortisol that produce or augment an insulin-resistant state. Relative insulin deficiency and excess catecholamines reduce glucose uptake by the ischemic myocardium and promote lipolysis and increased circulating free fatty acids. The latter inhibit glucose oxidation (the “glucose–fatty acid cycle”) and are toxic to ischemic myocardium, resulting in increased membrane damage, arrhythmias, and reduced contractility.

Alternatively, elevated blood glucose levels per se adversely affect outcome through the cumulative effects of several mechanisms, including induction of endothelial dysfunction, oxidative stress, hypercoagulability, and impaired fibrinolysis. However, the marked increase in risk for 30-day mortality with only mild elevations of FG argues against a toxic effect of elevated blood glucose, unless acceleration of these cellular alterations is exquisitely sensitive to small differences in plasma glucose levels. The finding that FG has a stronger association with mortality than known diabetes is also inconsistent with important detrimental effects of hyperglycemia.

**Study Limitations**

The prevalence of undiagnosed diabetes varies from 4% to 30% among patients admitted to the coronary care unit. Diabetes can be differentiated from stress hyperglycemia with certainty only after the acute phase of the infarction. Thus, any attempt to identify undiagnosed diabetes in our study would have been biased because patients must survive the acute phase to be diagnosed. It has been suggested that HbA1c be used to distinguish between stress hyperglycemia and hyperglycemia resulting from undiagnosed diabetes. However, there is a significant overlap in HbA1c levels between patients with acute myocardial infarction and known diabetes, newly diagnosed diabetes, and no diabetes. In addition, HbA1c is not recommended for the diagnosis of diabetes by recent guidelines even in stable subjects.

It has been suggested that undiagnosed diabetes may explain part of the mortality and morbidity associated with stress hyperglycemia. We addressed this possibility by comparing the outcome of patients with known diabetes and patients with no previous history of diabetes who presented with FG in the diabetic range in the entire study sample. By definition, all patients with undiagnosed diabetes are untreated and should have an FG level ≥126 mg/dL. However, the risk associated with prior diagnosis of diabetes was considerably lower compared with that of having FG in the diabetes range in the absence of prior diagnosis of diabetes. In this context, it is important to emphasize that a large number of studies in patients with acute myocardial infarction have shown that diabetes increases the risk of short-term mortality 1.5- to 2-fold. Thus, the presence of undiagnosed diabetes, if anything, would lead to an underestimation of true risk associated with stress hyperglycemia.

**Conclusions**

In nondiabetic patients with acute myocardial infarction, there is a graded relation between elevated FG and AG and 30-day mortality. FG is superior to random glucose measurement on admission with regard to the assessment of short-
term risk. FG concentrations may serve as a simple marker to help clinicians stratify risk for optimal triage and management.

References


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