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Original article

Association between elevated blood glucose level on admission and long-term mortality in patients with acute decompensated heart failure

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ABSTRACT

Background: The effect of elevated blood glucose (BG) levels on the long-term prognosis of acute decompensated heart failure (ADHF) patients has not been well defined. The purpose of this study is to evaluate the long-term prognosis of ADHF with elevated BG.
Methods: A cohort of patients consecutively admitted to the cardiac intensive care unit from 2007 to 2011 was studied. Among these, 495 patients who met the criteria were divided into 4 groups based on their BG level and diabetes mellitus (DM) status. The risks for all-cause mortality in each group were assessed using the multivariate Cox proportional hazards model.
Results: At a median follow-up of 1.8 years, 148 patients had died. There were 168 patients without either BG elevation or DM, 67 without BG elevation but with DM, 105 with BG elevation but not DM, and 155 with both BG elevation and DM. In a multivariate model, those with BG elevation, regardless of DM status, showed a greater risk of increased mortality when compared with patients without either BG elevation or DM [hazard ratio (HR), 1.79; $p = 0.042$ for BG elevation without DM and HR, 1.73; $p = 0.048$ for BG elevation with DM].
Conclusion: Elevated BG levels, irrespective of the DM status, at the time of admission in patients with ADHF, appear to be a prognostic marker for ADHF.

Introduction

Acute decompensated heart failure (ADHF) is a common reason for frequent hospital admission and has been associated with increased short-term mortality and poor long-term prognosis [1–4]. Increased early mortality in ADHF has been associated with altered cardiovascular physiology, such as hypotension, impaired renal function, impaired left ventricular function, and abnormal biomarkers [5–9]. The role of altered metabolic parameters as elevated blood glucose (BG) level has not been well defined in ADHF.

Elevated BG has been associated with poor outcomes in both, short- and long-term prognosis in various other clinical conditions, such as acute myocardial infarction, chronic obstructive pulmonary disease (COPD), cardiothoracic surgery, stroke, and other critical illnesses [10–14]. Few studies that looked at the outcomes of elevated admission BG in ADHF have shown conflicting results [6,15–20]. There are considerable variations among these studies in correct characterization of the diabetes patients, age difference, and inclusion of comorbid conditions limiting generalization. Furthermore, the relationship between BG level on hospital admission and long-term prognosis in patients with ADHF remains unclear.

In this study, we evaluated the long-term prognosis of ADHF in patients with elevated BG levels, irrespective of DM status, at the time of hospital admission for ADHF.

Methods

The Institutional Review Board of the Juntendo University Hospital approved the study protocol, and the study complied with

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the Declaration of Helsinki. Informed consent was obtained from all patients.

Study participants and inclusion criteria

Patients who were admitted to the cardiac intensive care unit in the Juntendo University Hospital, Tokyo, Japan from January 2007 to December 2011 were considered for the study. Among these, patients with a diagnosis of ADHF were included in the study except those meeting the exclusion criteria.

All eligible patients were divided into 4 groups based on their BG level on admission and DM status. The median value of BG level of 131 mg/dl was used as the cut-off value because there is no established cut-off value to define elevated BG levels on admission in patients with ADHF.

ADHF was defined based on modified Framingham criteria [21]. DM was defined as patients with earlier diagnosis of diabetes, on anti-diabetic medications, or glycosylated hemoglobin A1c (HbA1c) level ≥6.5% on admission, as defined by the National Glycohemoglobin Standardization Program (NGSP) [22]. A current smoker was defined as one who was smoking at the time of hospital admission or had quit smoking within 1 year at the time of admission.

Exclusion criteria

Patients who had acute coronary syndrome and/or had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization, had a life-threatening malignancy, on long-term hemodialysis, or had severe valvular heart disease were excluded from the study. Patients whose HbA1c levels were not measured on admission were also excluded.

Data collection

Baseline data were prospectively collected at the time of initial hospital admission. Medical history was obtained from patients' clinical chart review. BG on admission was measured by enzymatic methods regardless of their fasting status. HbA1c levels measured using Japan Diabetes Society (JDS) values were converted to NGSP values using the following equation: NGSP (%) = 1.02 × JDS (%) + 0.25% [22]. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with a Japanese coefficient from baseline serum creatinine levels [23]. Complete 2-dimensional echocardiography was performed on each patient. The left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson method.

All patients were followed up from the date of index admission until July 2013; outcome data were obtained by reviewing the medical records for all deaths recorded after discharge. The endpoint of interest was all-cause mortality.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) unless indicated otherwise, and were compared using one-way analysis of variance with Dunnett's test. The natural log-transformed values were used for statistical analyses of C-reactive protein (CRP), B-type natriuretic peptide (BNP), and BG levels, as the values were skewed. Categorical data were tabulated as frequencies and ratios (%), and were compared using the χ^2 test or Fisher's exact test with Bonferroni correction.

Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate the association between the categories of patients' groups and all-cause mortality.

On univariate analysis, one of the following was included as an independent variable: age, sex, body mass index (BMI), current smokers, history of heart failure (HF), ischemic heart disease, atrial fibrillation, history of COPD, systolic blood pressure, heart rate, LVEF, hemoglobin level, eGFR, sodium level, potassium level, CRP level, BNP level, and medications before admission, in addition, to the categories of patients' group. Variables that showed $p < 0.10$ on univariate analysis were entered into a multivariate Cox proportional hazards regression analysis. The assumption of proportional hazards was assessed using a log-minus-log survival graph. A p-value of <0.05 was considered statistically significant (for Bonferroni correction, this was based on adjusted p-values). All analyses were done using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 1684 patients were consecutively admitted to the cardiac intensive care unit from 2007 to 2011. There were 751 patients admitted to the cardiac intensive care unit due to ADHF. Among these, 234 patients who had acute coronary syndrome and/or had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization, had a life-threatening malignancy, on long-term hemodialysis, or had severe valvular heart disease were initially excluded and 22 patients who did not have HbA1c levels measured were then excluded. Finally, 495 patients were divided into 4 groups based on median BG level (≥131 mg/dl or less) on admission, and with presence or absence of DM as shown in Fig. 1.

The baseline characteristics of the patients are shown in Table 1. The percentage of patients with ischemic heart disease differed significantly across these groups. By definition, patients with BG elevation had greater BG levels on admission, and patients with DM had greater HbA1c levels. However, there were no other significant differences in baseline characteristics among these groups.

Outcomes

At a median follow-up of 1.8 years, 148 patients had died (29.9%). Forty-seven (28.0%) patients died without either BG elevation or DM; 17 (25.4%) died without BG elevation but with DM; 34 (32.4%) died with BG elevation but not DM; and 50 (31.3%) died with both BG elevation and DM.

In univariate analysis, groups with both BG elevation and DM and those with BG elevation but not DM showed an increased trend for mortality, compared with the group without either BG elevation or DM [hazard ratio (HR), 1.43; 95% confidence interval (CI), 0.96–2.14; $p = 0.079$, and HR, 1.29; 95% CI, 0.83–2.00; $p = 0.261$, respectively]; the mortality risk of the group without BG elevation but with DM was similar to that of the group without either BG elevation or DM (HR, 0.95; 95% CI, 0.54–1.65; $p = 0.852$). In addition, increased age (HR, 1.03; 95% CI, 1.02–1.05; $p < 0.001$), lower BMI (HR, 0.93; 95% CI, 0.88–0.97; $p = 0.001$), current smoker (HR, 1.36; 95% CI, 0.98–1.89; $p = 0.066$), history of HF (HR, 1.62; 95% CI, 1.17–2.25; $p = 0.004$), ischemic heart disease (HR, 1.49; 95% CI, 1.08–2.06; $p = 0.015$), atrial fibrillation (HR, 1.63; 1.13–2.36; $p = 0.010$), COPD (HR, 1.74; 95% CI, 0.91–3.33; $p = 0.092$), lower systolic blood pressure (HR, 0.99; 95% CI, 0.98–0.99; $p < 0.001$), lower hemoglobin level (HR, 0.81; 95% CI, 0.76–0.87; $p < 0.001$), lower eGFR (HR, 0.99; 95% CI, 0.98–0.99; $p < 0.001$), lower sodium level (HR, 0.95; 95% CI, 0.92–0.99; $p = 0.006$), greater CRP level (HR, 1.18; 95% CI, 1.07–1.31; $p = 0.001$), greater BNP level (HR, 1.35; 95% CI, 1.14–1.59; $p < 0.001$), and use of diuretics before admission

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