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Original article

Usefulness of the plasma glucose concentration-to-HbA_{1c} ratio in predicting clinical outcomes during acute illness with extreme hyperglycaemia

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Abstract

Aims. – To evaluate the correlation between the plasma glucose-to-glycated haemoglobin ratio (GAR) and clinical outcome during acute illness.

Methods. – This retrospective observational cohort study enrolled 661 patients who visited the emergency department of our hospital between 1 July 2008 and 30 September 2010 with plasma glucose concentrations > 500 mg/dL. Systolic blood pressure, heart rate, white blood cells, neutrophils, haematocrit, blood urea nitrogen, serum creatinine, liver function and plasma glucose concentration were recorded at the initial presentation to the emergency department. Data on glycated haemoglobin over the preceding 6 months were reviewed from our hospital database. The glucose-to-HbA_{1c} ratio (GAR) was calculated as the plasma glucose concentration divided by glycated haemoglobin.

Results. – The GAR of those who died was significantly higher than that of the survivors (81.0 ± 25.9 *vs* 67.6 ± 25.0; $P < 0.001$). There was a trend towards a higher 90-day mortality rate in patients with higher GARs (log-rank test $P < 0.0001$ for trend). On multivariate Cox regression analysis, the GAR was significantly related to 90-day mortality (hazard ratio [HR] for 1 standard deviation [SD] change: 1.41, 95% confidence interval [CI]: 1.22–1.63; $P < 0.001$), but not to plasma glucose (HR: 0.89, 95% CI: 0.70–1.13; $P = 0.328$). Rates of intensive care unit (ICU) admission and mechanical ventilator use were also higher in those with higher GARs.

Conclusion. – GAR independently predicted 90-day mortality, ICU admission and use of mechanical ventilation. It was also a better predictor of patient outcomes than plasma glucose alone in patients with extremely high glucose levels.

Keywords: Diabetes mellitus; Glucose-to-glycated haemoglobin ratio; Glycated haemoglobin; Stress-induced hyperglycaemia

1. Introduction

Stress-related hyperglycaemia is common among patients with acute illness, even in those without diabetes mellitus (DM). Acute hyperglycaemia is mediated by activation of inflammatory cytokines and other counterregulatory hormones, of which glucagon plays the most prominent role, but which also includes epinephrine, cortisol and growth hormones. A complex neurohormonal interplay leads to hepatic glucose production and insulin resistance, ultimately resulting in elevated plasma glucose concentrations [1–3].

Abbreviations: ANC, absolute neutrophil count; ANOVA, analysis of variance; AUC, area under the curve; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; eGFR, estimated glomerular filtration rate; GAR, glucose-to-glycated haemoglobin ratio; HbA_{1c}, glycated haemoglobin; Hct, haematocrit; HR, hazard ratio; ICU, intensive care unit; LDL-C, low-density lipoprotein cholesterol; ROC, receiver operating characteristic curve; SD, standard deviation; TC, total cholesterol; WBC, white blood cell count.

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Numerous observational studies have reported an association between elevated blood glucose levels and morbidity and mortality in hospitalized patients [4–9]. In addition, it has been reported that patients without underlying DM are more susceptible to morbidity and mortality when exposed to stress-related hyperglycaemia than those with a known medical history of DM [10–12]. Based on this finding, some researchers have suggested that the acute elevation of plasma glucose rather than hyperglycaemia itself plays a more prominent role in causing poor clinical outcomes [13,14].

The present retrospective cohort study was conducted to investigate this hypothesis. First, a novel index, the glucose-to-glycated haemoglobin (HbA_{1c}) ratio (GAR), was defined as the ratio of plasma glucose concentration to HbA_{1c}. The latter reflects the baseline average glucose status over the past 3 months. The GAR quantifies the extent of acute elevation in plasma glucose compared with background plasma glucose levels. The aim of the study was to evaluate whether the GAR has a better correlation with clinical outcomes than glucose concentration in patients presenting with extremely high glucose levels.

2. Methods

2.1. Study participants

The study recruited patients who presented to the emergency department (ED) of Taipei Veterans General Hospital between 1 July 2008 and 30 September 2010 for any reason. The inclusion criterion was a random plasma glucose concentration ≥ 500 mg/dL as measured within 24 h of arriving at the ED. Exclusion criteria were age < 30 years or > 99 years and death within < 24 h after ED arrival. HbA_{1c} data from 6 months prior to the ED visit were collected. For those with no available HbA_{1c} data, measurements of HbA_{1c} on the day of presentation to the ED or during the hospital stay were allowed. A total of 781 patients visited the ED with blood glucose concentrations > 500 mg/dL, but 25 were excluded due to their age, 23 died within 24 h and 72 had no HbA_{1c} data for the past 6 months or from their ED and/or hospital stay. The remaining 661 patients were enrolled for further analyses (Fig. S1; see supplementary material associated with this article online).

2.2. Baseline characteristics

Baseline demographic and biochemical data of the 661 enrolled patients were obtained from the ED. History of DM, reason for ED admission, length of stay and cause of death were recorded. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Our hospital database for HbA_{1c} data over the past 6 months was reviewed. If there was more than one entry, only the entry closest to the time of ED presentation was used for the analysis. Among patients with no known DM and no available HbA_{1c} data, HbA_{1c} measurement was performed at our ED or after admission. The GAR was calculated using the following formula: GAR = random plasma glucose concentration (mg/dL) $\div$ HbA_{1c} (%). The patients were then stratified into four groups by quartiles of GAR (Q1–Q4) for further comparisons.

2.3. Measurement of serum glucose levels and HbA_{1c}

Glucose and HbA_{1c} measurements were performed at the central laboratory of Taipei Veterans General Hospital. Glucose was measured by a cobas c702/c501 analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland) using the hexokinase/glucose-6-phosphate dehydrogenase method. HbA_{1c} assays were performed using an automated blood analyzer (HLC-723 G7/G8, Tosoh Corporation, Tokyo, Japan) equipped with a cation-exchange high-performance liquid chromatography system.

2.4. Outcomes

The primary outcome was death from any cause within 90 days. The exact date of death was obtained from the Department of Health, Executive Yuan, ROC (Taiwan). Secondary outcomes included admission to the intensive care unit (ICU) and frequency of respiratory failure, defined as the need for mechanical ventilatory support.

2.5. Statistical analysis

All statistical analyses were performed using SPSS software for Windows, version 20.0 (SPSS Institute, Inc., Chicago, IL, USA). Baseline characteristics were compared between survivors and non-survivors, and across the four quartiles (Q1–Q4) of GAR. Continuous data were analyzed using Student's t test and one-way analysis of variance (ANOVA), and expressed as means $\pm$ standard deviation (SD). Nominal and ordinal data were compared using Pearson's χ^2 test between groups and reported as percentages.

Variables showing significant differences between the survivors and non-survivors and between GAR quartiles were further examined using univariate and multivariate logistic-regression analyses. The results are presented as the hazard ratio (HR) of incidence per 1 SD and 95% confidence interval (CI). The survival analysis and log-rank test were used to evaluate the trend of association between GAR quartile and 90-day mortality rate. To evaluate the performance of GAR in predicting the 90-day mortality rate, receiver operating characteristic (ROC) curves and the respective areas under the curve (AUCs) analysis were calculated for each variable. Rates of mechanical ventilator use and ICU admission were compared across Q1–Q4 using ANOVA. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics according to GAR

The patients were divided evenly into four quartiles according to GAR, and their baseline characteristics were compared

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