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Original Article

Long-term outcomes in older patients with hyperglycemia on admission for ischemic stroke

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ABSTRACT

Aims: Evaluate the association between admission blood glucose (ABG) and mortality in older patients with or without diabetes mellitus (DM) hospitalized for acute ischemic stroke (AIS).
Methods: Observational data of patients ≥65 years, admitted for AIS between January 2011 and December 2013. ABG levels were classified to categories: ≤70 (low), 70–110 (normal), 111–140 (mildly elevated), 141–180 mg/dl (moderately elevated) and >180 mg/dl (markedly elevated). Main outcome was all-cause mortality at the end-of-follow-up.
Results: Cohort included 854 patients, 347 with (mean ± SD age 80 ± 8, 44% male), and 507 without DM (mean ± SD age 78 ± 8, 53% male). There was a significant interaction between DM, ABG and mortality at end-of-follow-up ($p \le 0.05$). In patients without DM there was a dose-dependent association between ABG category and mortality: adjusted hazard ratios (95% CI) compared to normal ABG were 1.8 (1.2–2.8), 2.9 (1.6–5.2) and 4.5 (2.1–9.7), respectively, for mildly, moderately and markedly elevated ABG. In patients with DM there was no association between ABG and mortality. There was no interaction between DM, ABG and in-hospital mortality or length of stay (LOS). Irrespective of DM status, compared to normal ABG levels, increased ABG category was associated with increased in-hospital mortality: adjusted odds ratios were 3.9 (1.1–13.4), 7.0 (1.8–28.1), and 20.3 (4.6–89.6) with mildly, moderately and markedly elevated ABG, respectively. Mean LOS was 6 ± 5, 7 ± 8, 8 ± 7, and 8 ± 8 days, respectively.
Conclusion: In older patients without DM hospitalized for AIS, elevated ABG is associated with increased long-term mortality. Irrespective of DM status, elevated ABG was associated with increased in-hospital mortality and LOS.

1. Introduction

Admission hyperglycemia is commonly observed in patients hospitalized for acute ischemic stroke (AIS) [1–9]. Many patients with hyperglycemia have underlying or newly diagnosed diabetes mellitus (DM), which is a well-established risk factor for AIS [10]. In AIS patients without DM, as in other serious illnesses, elevated admission blood glucose (ABG) levels may be the result of stress-mediated activation of sympathetic nervous system and hypothalamic-pituitary-adrenal axis and release of proinflammatory cytokines such as interleukins 1 and 6 and tumor releasing factor [11].

Hyperglycemia is considered a poor prognostic factor in AIS. Several [1–3,5], but not all [8–9] studies have reported an association between admission hyperglycemia and longer hospitalization time and increased in-hospital and short-term post hospitalization mortality. Elevated ABG levels were also related to increased functional impairment [4–7]. In a systematic review and meta-analysis of the literature, the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level > 144 mg/dl was 3.07 in patients without DM [12].

Limited data are available regarding the long-term outcomes of elevated ABG levels in older patients hospitalized for AIS [13,14]. Therefore, in this study we aimed to evaluate the association between ABG levels in older patients with and without DM and long-term all-cause mortality following hospitalization for AIS.

2. Methods

The present retrospective observational study was conducted at Rabin Medical Center in Israel, a 1300-bed university-affiliated tertiary hospital. Most of the patients in its 10 medical wards are admitted through the emergency department. All patient data are recorded in

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electronic medical charts based on the same database platform used in the community primary care facilities. Mortality data are recorded in the hospital's mortality database, updated from the Population Registry of the Israel Ministry of the Interior.

The study group included all patients aged 65 years or more, who were admitted to the medical wards of Rabin Medical Center between January 1, 2011 and December 31, 2013 and had a principal discharge diagnosis of ischemic stroke. The study did not include patients with a diagnosis of transient ischemic attack. All diagnoses of ischemic stroke were based on an evaluation by a trained neurologist, clinical, laboratory and imaging studies. In cases of recurrent admissions during the study period, only the initial one at which ischemic stroke was diagnosed was included in the analysis. Patients without documented ABG levels were excluded. Mortality data were collected until February 1, 2017. The study was approved by the Institutional Review Board of Rabin Medical Center.

Patients were stratified into those with pre-existing DM, if their medical record included a diagnosis of DM or use of any oral hypoglycemic agent, glucagon-like peptide agonist, or insulin at the time of admission, and those without DM.

ABG levels, defined as the blood glucose level closest to the patient's admission and, within the first 24 h of the admission date, were classified into the following five categories: <70, 70 to 110, 111 to 140, 141–180, and >180 mg/dl. These categories were chosen in accordance with the American Diabetes Association guidelines, which recommend initiating insulin therapy for treatment of persistent hyperglycemia starting at a threshold of 180 mg/dl and above, aiming at a target glucose range of 140–180 mg/dl for critically and non-critically ill patients [11].

Blood glucose measurements were based on serum glucose levels derived from venous blood samples.

We have collected data regarding co-morbidities, according to diagnoses as defined in the medical records, including: malignancy, hyperlipidemia, hypertension, ischemic heart disease, chronic heart failure, chronic renal failure, chronic obstructive pulmonary disease, and inflammatory bowel disease.

2.1. Statistical analysis

The statistical analysis was generated using SAS Software, version 9.4 of the SAS System for PC, Copyright 2002–2012. SAS Institute Inc. and all other SAS Institute Inc. products or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Continuous variables were presented by mean ± SD, categorical variables were presented by (n, %). *T*-Test was used to compare the value of continuous variables between study groups and Chi-Square was used to value of categorical variables between study groups. Cox proportional hazards model was used to assess the effect of study variables on survival, including age, gender, smoking, alcohol, BMI, malignancy, chronic renal failure, ischemic heart disease, congestive heart failure, hypertension, as well as for interaction between DM and glucose levels. As there was an interaction between DM, ABG and long-term mortality ($p < 0.05$), we analyzed the data and ran the Cox model separately for patients with DM and patients without DM. However, as there was no interaction between ABG, DM, and in-hospital mortality or length of stay, in that case we analyzed the data for the entire cohort, irrespective from DM status.

We had complete data for all the study variables, other than BMI, smoking and alcohol. The data analysis at the end-of-follow-up included all fatality cases from admission until the end-of-follow-up. No imputation for missing data was done because missing at random cannot be assumed. Due to the small number of patients with low ABG levels, we did not analyze the data for this group.

3. Results

3.1. Study cohort

There were a total of 73,796 admissions to the medical wards of Rabin Medical Center during the study period. We identified 865 patients ≥65 years of age with a principal discharge diagnosis of ischemic stroke. We excluded 11 patients because of missing ABG data (n = 2) or ABG level < 70 mg/dl (n = 9). The final cohort consisted of 854 patients, 408 male (48%) and 446 female of median age on admission 79 ± 8 years (65–108 years); 347 patients (41%) had pre-existing DM (mean ± SD age 80 ± 8, 44% male) and 507 did not (mean ± SD age 78 ± 8, 53% male).

3.2. Patient characteristics by ABG categories

In the entire cohort, most of the patients had ABG levels of <140 mg/dl: 32%, 70–110 mg/dl (normal) and 31%, 111–140 mg/dl (mildly elevated). ABG levels of ≥180 mg/dl were documented in 159 patients (19%), most of whom had pre-existing diabetes (82%). Patients with an ABG level of >180 mg/dl had significantly higher rates of hypertension, ischemic heart disease, and chronic renal failure, than patients with an ABG level of 70–110 mg/dl (Table 1). Most patients without DM had normal ABG levels (43%) or mildly elevated ABG levels (39%) (Fig. 1).

Glycated hemoglobin in the 12 months prior to hospitalization were available for half of the patients with DM (175/374 patients). Mean ± SD glycated hemoglobin were 7.0 ± 1.0%, 7.0 ± 0.9, 7.8 ± 1.3%, and 8.6 ± 2.0% in patients with normal ABG, mildly, moderately and markedly increased ABG levels, respectively. Glycated hemoglobin data were available for a minority of the patients without DM (70/507 patients) with mean ± SD levels of 6.2 ± 0.8%.

3.3. Mortality at the end-of-follow-up by ABG categories

As there was an interaction between DM, ABG and mortality at the end-of-follow-up, we analyzed the data separately in patients with and without DM. While there was an association between ABG and long-term mortality in patients without DM ($p < 0.01$), there was no similar association in patients with DM.

We had complete follow-up data at 12 months for all patients, and the median ± SD follow-up time from admission was 4.5 ± 0.9 years. The data analysis at the end-of-follow-up included all fatality cases from admission until the end-of-follow-up. At the end of follow-up mortality rate in the entire group of patients without DM was 40%

Table 1
Baseline characteristics of patients with and without diabetes mellitus. BMI – body mass index. *p < 0.05.

	Patients without diabetes mellitus (n = 507, 59%)	Patients with diabetes mellitus (n = 347, 41%)
Patient characteristics		
Age, mean ± SD (median)	80 ± 8 (81)	78 ± 8 (77) *
Men, n (%)	223 (44%)	185 (53%)*
Smoking (%)	57 (8%) (Missing = 37)	42 (13%)* (Missing = 27)
Alcohol (%)	8 (2%) (Missing = 42)	4 (1%) (Missing = 30)
BMI, mean	26 ± 4	29 ± 4*
Co-morbidities, n (%)		
Malignancy	58 (11%)	37 (11%)
Hypertension	302 (60%)	261 (75%)*
Ischemic heart disease	89 (18%)	115 (33%)*
Congestive heart failure	35 (7%)	23 (7%)
Chronic renal failure	31 (6%)	40 (12%)*
Chronic obstructive Pulmonary disease	12 (2%)	6 (2%)

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