Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Blood glucose on admission and mortality in patients with venous thromboembolism

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ARTICLE INFO

Article history:
Received 11 May 2016
Received in revised form 16 June 2016
Accepted 18 June 2016
Available online xxxx

Keywords:
Admission
Diabetes mellitus
Deep vein thrombosis
Mortality
Pulmonary embolism

ABSTRACT

Aims: Evaluate association between admission blood glucose (ABG) and mortality in patients with or without diabetes mellitus (DM) hospitalized for venous thromboembolism (VTE).
Methods: Observational data derived from the electronic records of hospitalized patients ≥18 years, admitted for VTE (including deep vein thrombosis and pulmonary embolism) 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. We had complete follow-up data at 12 months for all patients; median follow-up time was 1126 days.
Results: Cohort included 567 patients, 137 with (mean age 73, 45% male), and 430 without DM (mean age 65, 40% male). There was a significant interaction between DM, ABG and mortality ($p \le 0.05$). In patients without DM there was a significant association between ABG and mortality: [hazard ratios 1.6, 2.3, and 4.7 respectively for mildly, moderately and markedly elevated ABG ($p \le 0.01$)]. A significant association between ABG and mortality persisted following multivariable analysis only in patients with markedly elevated ABG (HR = 2.3 95% CI 1.2–4.5). Similar results were evident in patients with deep vein thrombosis or pulmonary embolism. In patients with DM there was no significant association between ABG and mortality.
Conclusion: In patients without DM hospitalized for VTE, markedly elevated ABG is associated with increased mortality.

1. Introduction

Hyperglycemia is associated with elevated coagulation factors and impaired fibrinolysis, and previous studies reported association of hyperglycemia with an increased risk of venous thromboembolism (VTE) (Lemkes et al., 2010). The estimated incidence rate of VTE is 75–269 cases per 100,000 individuals in Western Europe, North America, Australia, and Southern Latin America, and pulmonary embolism represents one third of all VTE cases (Raskob, Angchaisuksiri, Blanco, et al., 2014).

Elevated admission blood glucose (ABG) levels during acute illness is common and is associated with poor outcomes among patients with and without diabetes following admission for several conditions including ischemic or hemorrhagic stroke (Capes, Hunt, Malmberg, Pathak, & Gerstein, 2001), surgery (Golden, Linda, & Frederick, 1999), trauma (Yendamuri, Fulda, & Tinkoff, 2003), heart failure (Barsheshet, Garty, Grossman, et al., 2007; Kosiborod, Inzucchi, Spertus, et al., 2009), pneumonia (Akirov & Shimon, 2016; Falciglia et al., 2009; Foltran, Gregori, Caropreso, Pagano, & Bruno, 2013; Gamble, Eurich, Marrie, & Majumdar, 2010) and acute myocardial infarction (Capes, Sarah, & Hertzel, 2000; Timmer, van der Horst, Ottervanger, et al., 2004; Yang, Song, Bin, et al., 2013).

ABG values are readily available for most hospitalized patients, and may predict the short and long-term outcomes of patients hospitalized for VTE. Our objective was to evaluate the association between ABG levels in patients with and without DM and all-cause short and long-term outcomes following hospitalization for VTE.

2. Methods

Historical prospective data were extracted from the electronic medical records of all patients who were admitted to the medical wards in Rabin Medical Center, Israel, between January 1, 2011 and December 31, 2013. Inclusion criteria were age ≥18 years with a principal discharge diagnosis of pulmonary embolism (PE) or deep

The authors report no conflict of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2016.06.019
1056-8727/

vein thrombosis (DVT). Diagnosis of PE/DVT was based on medical history, physical examination, laboratory results and imaging studies, including Doppler ultrasound, computed angiography, or, in rare cases, lung ventilation/perfusion scan. We did not include cases of superficial vein thrombosis. In case of a recurrent admission for VTE, the first admission in that time period was considered the index hospitalization and the recurrent admission was excluded from the data analysis. Patients without documented ABG levels were excluded.

Rabin Medical Center, encompassing Beilinson and Golda-Hasharon campuses, is a tertiary-care facility with more than 1300 beds. Most of the admissions to the 10 medical wards are through the emergency department, and all patients' data are recorded in electronic medical charts, based on the same database platform used in community primary care facilities. Mortality data were obtained from the hospital's mortality database, updated from the Ministry of the Interior Population Registry. We collected mortality data until June 1, 2015.

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 (American Diabetes Association, 2016).

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, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, interstitial lung 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. Normal distribution of continuous variables (age, BMI) was confirmed using and parametric (Kruskal–Wallis) and nonparametric (Wilcoxon) and nonparametric tests. Cox proportional hazards model was used to assess the effect of study variables on survival, including age, gender, smoking, alcohol, malignancy, chronic renal failure, ischemic heart disease, congestive heart failure, hypertension, and cerebrovascular disease, as well as for interaction between DM and glucose levels. Since this interaction was significant ($p \le 0.05$), the Cox model was rerun by DM groups. This analysis proved a significant association between ABG levels and mortality risk in patients without DM, but in the group of patients with DM there was no significant association ($p > 0.05$). Subsequently, we focused our data analyses on the group of patients without DM.

We had complete data for all the study variables, other than BMI and smoking. 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

Amongst 35,340 patients admitted to the medical wards during the study period, including 24,159 without DM (68%) and 11,181 with DM (32%), the final cohort comprised 567 patients admitted with VTE, including 295 cases with deep vein thrombosis (DVT), 277 cases with pulmonary embolism (PE), including 5 cases with both DVT and PE (Fig. 1).

Mean ± SD age of the cohort was 67 ± 18 years (range 19–99 years), 232 were men (41%) and 430 (76%) did not have pre-existing DM. Data on DM type were available for 100 of the 137 (73%) patients with DM, and all had type 2 DM. In the remainder, type 2 DM was likely in most cases but this could not be confirmed. Compared with patients without DM, those with DM were older (mean age 65 ± 19 vs. 73 ± 12, $p < 0.001$). Malignancy rates were comparable in patients with and without DM (30% vs., 26%, $p > 0.05$). Rates of hypertension, hyperlipidemia, ischemic heart disease and cerebrovascular disease were significantly higher in the group of patients with pre-existing DM (Table 1). As expected, malignancy rates were much higher in the group of patients with VTE (151/567, 27%) compared with hospitalized patients without VTE (5,080/34,773, 15%).

Most patients without DM had normal ABG levels (52%) or mildly elevated ABG levels (31%), while markedly elevated ABG levels were much less common (5%). However, most of the patients with DM had markedly elevated ABG levels (44%), or moderately elevated ABG levels (24%). The total number of patients with low ABG levels was very small (4 patients without DM and 3 patients with DM (Fig. 1).

We had complete follow-up data at 12 months for all patients, with first patient censored after 519 days. Median follow-up time was 1126 days.

In-hospital mortality rates were 6%, with mortality rates of 13% at 30-days after discharge, 26%, 31% and 34% mortality rates 12-, 24- and 36-months after discharge. Mortality rates were higher in the group of patients with DM, compared with patients without DM throughout the follow-up period (Fig. 2). At the end of follow up mortality rates were 39% (223/567 patients). Mortality rates were highest in the group of patients with markedly elevated ABG levels and lowest in the group of patients with normal ABG levels, compared with all other ABG categories (Fig. 3).

In the group of patients with DM there was no significant association between ABG levels and mortality rates ($p > 0.05$). In patients without DM, there was a statistically significant association between ABG and mortality risk ($p < 0.0001$ for all comparisons).

Unadjusted hazard ratios (95% CI) of all-cause mortality at the end of follow-up, compared with normal ABG levels were 1.6 (1.1–2.4) for mildly elevated ABG levels, 2.3 (1.4–3.7) for moderately elevated ABG, and 4.7 (2.7–8.1) for markedly elevated ABG levels.

Following adjustment for age, gender, smoking, alcohol, malignancy, ischemic heart disease, congestive heart failure, hypertension, chronic renal failure and cerebrovascular disease, the adjusted hazard ratios (95% CI) of all-cause mortality, compared with normal ABG levels were 1.0 (0.7–1.5) with mildly elevated ABG levels, 1.6 (0.9–2.7) with moderately elevated ABG levels and 2.3 (1.2–4.5) with markedly elevated ABG.

Survival analysis at the end of follow-up demonstrated the highest survival rates following discharge for patients with normal or mildly elevated ABG levels, and lowest in patients with markedly elevated ABG levels ($p < 0.001$) (Kaplan–Meier analysis of patient survival following admission as time until death is shown in Fig. 4).

3.2. DVT

Our cohort included 295 patients with DVT, most of them without DM (224 patients, 76%). Rates of DVT during the study period were 0.8% (0.9% in patients without DM and 0.6% in patients with DM).

Please cite this article as: Akirov, A., et al., Blood glucose on admission and mortality in patients with venous thromboembolism, *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.06.019