Original Article

The impact of glycemic variability on length of stay and mortality in diabetic patients admitted with community-acquired pneumonia or chronic obstructive pulmonary disease

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ABSTRACT

Aim: To investigate the influence of glycemic variability (GV) on length of stay and in-hospital mortality in non-critical diabetic patients.

Methods: A observation retrospective study was performed. Diabetic patients admitted between January and June 2016 with the diagnosis of community-acquire pneumonia (CAP) and/or acute exacerbation of chronic obstructive pulmonary disease (COPD) were enrolled and glycemic control (persistent hyperglycemia, hypoglycemia, mean glucose level (MGL) and respective standard deviation (SD) and coefficient of variation (CV)) were evaluated. Primary outcomes were length of stay and in-hospital mortality.

Results: Data from 242 patients were analyzed. Fifty-eight percent of the patients were male, with a median age of 77 years (min-max, 29–98). Patients had on average 2.1 glucose readings-day and the MGL was 193.3 mg/dl (min-max, 84.3–436.6). Hypoglycemia was documented in 13.4% of the patients and 55.4% had persistent hyperglycemia. The median length of hospital stay was 10 days (min-max, 1–66) and in-hospital mortality was 7.4%. We found a significant higher in-hospital mortality in older patients, with history of cancer and with nosocomial infections. We did not find any correlation between MGL, SD, CV, hypoglycemia or persist hyperglycemia and in-hospital mortality. A longer length of stay was observed in patients with heavy alcohol consumption and nosocomial infections. The length of stay was negatively correlated with the mean glucose level (r^2-0.147; $p < 0.05$) and positively correlated with the coefficient of variation (p 0.162; $p < 0.05$).

Conclusion: This study confirmed the negative impact of the glycemic variability in the outcomes of diabetic patients admitted with CAP or acute exacerbation of COPD.

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1. Introduction

The prevalence of diabetes mellitus (DM) has been steadily increasing over the past few decades, promoted by the global rise in the prevalence of obesity and unhealthy lifestyles. The latest report from the World Health Organization (WHO) estimates a global prevalence of 422 million people living with diabetes in 2014 [1]. Patients with diabetes mellitus have highest rates of hospitalization and increased risk of adverse outcomes and mortality [2,3].

Over time, diabetes can lead to serious complications, including macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular disease (diabetic nephropathy, retinopathy and neuropathy). The lung is also a target organ for diabetic microangiopathy and several studies have demonstrated that pulmonary function tests are significantly decreased in subjects with DM in comparison to healthy controls [4–6]. Decrements in the lung function of patients with diabetes are believed to be the consequence of biochemical alterations in the connective tissue constituents of the lung, particularly collagen and elastin, as well as microangiopathy due to the nonenzymatic glycosylation of proteins induced by chronic hyperglycemia [7]. A large cohort study involving 1,811,228 individuals reported an increased risk of several pulmonary conditions, such as asthma, chronic obstructive

pulmonary disease (COPD) and pneumonia among individuals with diabetes [8]. There is also evidence of greater susceptibility to bacterial infection in diabetic patients specially those suffering from COPD [9].

Hyperglycaemia has been associated with a poor outcome from a wide range of acute illnesses, including community-acquired pneumonia (CAP) and COPD [10,11]. Hypoglycemia has also been independently associated with a significant increase in adverse outcomes in hospitalized patients [12,13].

In the last years, some studies have showed that acute fluctuations of glucose exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia and seem to have more deleterious effects in the development of diabetic complications [14]. In this regard, a third metric of glucose control, known as glycemic variability (GV), has been proposed to be additionally implicated in the disease-associated process of dysglycemia [15]. Data from the Verona Diabetes Study and the Taichung Diabetes Study have showed that glycemic variability, defined as the standard deviation (SD) of each patient's mean glucose level (MGL) was an independent predictor of mortality in type 2 diabetes patients [16–18] and studies in critically ill patients have demonstrated that increased GV is a strong, independent predictor of mortality [19,20].

The present study aims to investigate the influence of GV length of stay and in-hospital mortality in non-critical patients with previous diagnosis of DM admitted due to CAP or acute exacerbation of COPD.

2. Methods

After ethical approval was granted by the Ethics Committee of Centro Hospitalar do Porto, an observational retrospective study was conducted retrieving clinical data from medical records of patients admitted to the internal medicine services of Centro Hospitalar do Porto, between January and June 2016.

Patients with previous history of DM and admitted with the diagnosis of CAP and/or acute exacerbation of COPD were enrolled. Patients with less than three glucose readings during the hospital stay and with prolonged hospitalization for social causes were excluded. Patients who were hospitalized more than once had each admission counted separately.

Data were extracted from SClinico Hospitalar®. Demographic and clinical variables analyzed included age, gender, BMI, HbA1c, previous pharmacological treatment for diabetes, presence of ischemic heart disease, chronic kidney disease (stages 3, 4 or 5), presence of hypertension, dyslipidemia, smoking and alcohol habits, history of cancer and nosocomial infections. Heavy alcohol consumption was considered if intake >21 units-week. Glucose lowering therapy and glucocorticoid therapy during hospital stay were also reported.

The outcomes measured were length of stay (calculated by the number of days from admission date to discharge or death date) and in-hospital mortality.

Blood glucose concentrations were measured in capillary blood obtained by finger stick with a point-of-care device. Number of readings per patient-day, episodes of hypoglycemia and persistent hyperglycemia were evaluated. Hypoglycemia was defined as any episode of blood glucose less than 70 mg/dL during the hospital stay and persistent hyperglycemia was considered when blood glucose was above 180 mg/dL in more than 50% of the readings. MGL, SD of each patient's MGL and coefficient of variation (CV) of glucose (SD/MGL, [%]) was derived for each patient.

Statistical analysis was performed using SPSS, version 22.0. Data are presented as proportions, means (SD), or, in the case of variables that did not conform to a normal distribution, median (range). For independent samples, two-way comparisons for proportions were performed by chi-square test (X^2) for categorical variables and Mann−Whitney U test for continuous variables. Pearson and Spearman tests were used to assess associations between measures of GV and the two outcomes. Statistical significance was taken as two-tailed at the 0.05 level.

3. Results

During the study period, 363 individuals with DM were admitted due to CAP and/or acute exacerbation of COPD. After applying the exclusion criteria, a final sample of 242 patients was obtained. Fifty-eight percent of the patients were male, with a median age of 77 years (min-max, 29–98). The majority was previously treated only with oral antidiabetic drugs (53% vs 42% with insulin or both) and median HbA1c was 7.1% (min-max, 5.1–13.3). The diagnosis that motivated the admission was CAP in 55.6% and acute exacerbation of COPD in 44.4%. Additional demographic information is reported in Table 1.

Patients had on average 2.1 glucose readings per day (min-max, 0–24) and the mean glucose level was 193.3 mg/dl (min-max, 84.3–436.6). Hypoglycemia was documented in 33 (13.4%) patients and 134 (55.4%) had persistent hyperglycemia.

The median length of hospital stay was 10 days (min-max, 1–66) and 18 patients died during the hospitalization (in-hospital mortality 7.4%). We found a significant higher in-hospital mortality in older patients (p < 0.001), with history of cancer (61.1% vs 16.7%, p < 0.001) and with nosocomial infections (80% vs 20%,p < 0.05). We did not find any correlation between MGL, SD, CV, hypoglycemia or persist hyperglycemia and in-hospital mortality (Table 1).

As presented in Table 2, a longer length of stay was observed in patients with heavy alcohol consumption (11.5 vs 10 days, p < 0.05) and nosocomial infections (21 vs 10 days, p < 0.05). The length of stay was negatively correlated with the mean glucose level (r^2-0.147; p < 0.05) and positively correlated with the coefficient of variation (p 0.162; p < 0.05). We did not found correlation with any other variable, namely SD (see Table 3).

4. Discussion

In the present study, the length of stay and in-hospital mortality was studied in a population of diabetic patients admitted with CAP and/or exacerbation of COPD. The male preponderance and the high prevalence of comorbidities are consistent with data reported from other populations with COPD and diabetes [21–23].

It is well documented across the world the high burden of diabetes in hospitalized patients [24–26]. Patients with diabetes have a 3-fold greater chance of hospitalization, with greater costs, length of hospital stay, morbidity and mortality compared to those without diabetes [27].

In our cohort, 41% of the patients had an HbA1c higher than 8%, indicative of poor glycemic control. The high number of missings in this parameter should also be mentioned, which is not in line with current American Diabetes Association (ADA) guidelines that recommends the determination of HbA1c in all patients with diabetes admitted to the hospital if not performed in the prior 3 months [28].

In most instances in the hospital setting, insulin is the preferred treatment for glycemic control [29], however in this study, half of the patients continued on treatment with oral antihyperglycemic drugs. In this population this is particularly dangerous given the increased risk of hypoxia and consequent lactic acidosis reported in patients with acute COPD and CAP, as well as nephrotoxicity and hepatotoxicity, when associated with other drugs such as antibiotics [30].

Table 1
Demographic and clinical characteristics of patients and comparative analysis according to in-hospital mortality.

	N	Total (N, %)	In-Hospital Mortality		
			Yes (N, %)	No (N, %)	P[d]
Female gender	242	102 (42.1%)	9 (50.0%)	93 (41.5%)	0.483
Age (years)[a]	242	77.0 (29–98)	86.5 (62–96)	75.5 (29–96)	<0.001
BMI[b]	167	25.7 ± 0.4	25.5 ± 3.5	24.9 ± 5.2	0.345
Chronic kidney disease	242	94 (38.8%)	8 (44.4%)	85 (38.3%)	0.390
Ischemic heart disease	242	75 (31.0%)	5 (27.8%)	70 (31.5%)	0.741
Hipertension	242	199 (82.2%)	16 (88.8%)	181 (81.5%)	0.340
Dyslipidemia	242	156 (64.5%)	12 (66.6%)	143 (64.9%)	0.848
Smoking	242	96 (39.7%)	5 (27.8%)	91 (40.5%)	0.287
Heavy alcohol consumption	242	19 (7.9%)	–	19 (8.5%)	–
History of cancer	242	49 (20.2%)	11 (61.1%)	37 (16.7%)	<0.001
Nosocomial infection	242	20 (8.1%)	16 (80.0%)	4 (20.0%)	<0.05
HbA1c (%)[a]	143	7.1 (5.1–13.3)	6.5 (5.7–7.0)	7.0 (5.3–11.3)	0.430
Basal insulin therapy during hospitalization	242	213 (88.0%)	16 (80.0)	197 (87.9%)	0,576
Glucocorticoid therapy during hospitalization	242	121 (50.0%)	11 (61.1%)	110 (49.5%)	0.416
Mean glucose level (mg/dl)[a]	242	193.3 (84–436)	194 (84–209)	187 (109–436)	0.243
SD[a]	242	60.4 (2.8–144)	43 (2.8–85.4)	57 (15.3-144-2)	0.298
CV[b]	242	30.7 ± 6.8	24,2 ± 13.9	30,0 ± 11.1	0.532
Hipoglycemia	242	33 (13.6%)	2 (11.1%)	31 (14.8%)	0.538
Persistent hyperglycemia[c]	242	134 (55.4%)	10 (55.5%)	124 (55.3%)	0.584
Total	242		18 (7.4%)	224 (92.6%)	

SD – Standard deviation; CV - coefficient of variation.
[a] (median, range).
[b] (mean, SD).
[c] Persistent hyperglycemia blood glucose above 180 mg/dL in more than 50% of the readings.
[d] Chi-square test (X^2) for categorical variables and the Mann- Whitney test for continuous variables.

Table 2
Bivariate analysis on length of stay.

	Length of hospitalization stay (days)[a]		
	Yes	No	P[b]
Female gender	10 (2–64)	11 (1–43)	0.557
Chronic kidney disease	10.5 (2–43)	10 (1–64)	0.302
Ischemic heart disease	11 (3–39)	10 (1–64)	0.729
Hipertension	10 (2–43)	11.5 (1–64)	0.672
Dyslipidemia	10 (1–43)	11.5 (3–64)	0.059
Smoking	10 (1–64)	11 (1–43)	0.543
Heavy alcohol consumption	11.5 (3–64)	10 (1–43)	<0.05
History of cancer	14 (2–43%)	10 (1–64)	0.119
Nosocomial infection	21 (9–40)	10 (1–64)	<0.001
Basal insulin therapy during hospitalization	12.5 (5–39)	10 (1–64)	0.090
Glucocorticoid therapy during hospitalization	11 (2–40)	10 (1–64)	0.995
HbA1C >8%	11 (2–43)	0 (1–64)	0.244
Hipoglycemia	2 (11.1%)	31 (14.8%)	0.538
Persistent hyperglycemia	10 (55.5%)	124 (55.3%)	0.584

[a] (median, range).
[b] Mann-Whitney.

Table 3
Spearman and Pearson analysis on length of stay.

	x length of stay
	Correlation coefficient
Age[a]	0.26
Mean glucose level (mg/dl)[a]	−0.147**
SD[a]	0.07
CV[b]	0.162**

SD – Standard deviation; CV - coefficient of variation.
**p < 0.005.
[a] Sperman test.
[b] Pearson test.

Extensive data indicates that inpatient hyperglycemia, is associated with poor clinical outcomes, such as mortality, infections and hospital complications [26,31–33]. On the other hand, studies have shown that intensive insulin therapy in hospitalized patients is associated with increased risk of hypoglycemia, which has been associated with increased morbidity and mortality [12,13,34]. Therefore, recommendations regarding glycemic goals within the hospital setting have changed over the last two decades and, nowadays, the standard is to initiate insulin therapy for persistent hyperglycemia greater than 180 mg/dL and once insulin therapy is initiated, a glucose target of 140–180 mg/dL is recommended for most critically ill patients and noncritically ill patients [28]. In this study, more than half of the patients (55.4%) had persistent hyperglycemia (>180 mg/dL) during hospitalization, with a mean glucose level of 193.3 mg/dl, suggesting a poor glycemic control of hospitalized patients. There are many reasons why ill patients develop hyperglycemia. Inflammatory cytokines and stress hormones inhibit insulin release and promote insulin resistance, thereby naturally increasing blood glucose. In addition, many medical therapies further promote hyperglycemia, including the

administration of exogenous catecholamines and corticosteroids, the infusion of dextrose or providing parenteral nutrition [35]. At least one episode of hypoglycemia was documented in 13.4% of the patients. Hypoglycemia was more frequent in patients with intensive insulin treatment (22.4% vs 8.1%, p < 0.05). In this cohort, however, we did not found an association between these two variables (persistent hyperglycemia and hypoglycemia) and longer length of stay or increased in-hospital mortality.

Bed side blood glucose monitoring allows the evaluation of the patient's response to treatment and compliance with glycemic goals. In hospitalized diabetic patients, bed side glucose monitoring should be performed before meals or every 4–6 h if the patient is not eating [28,29]. We documented a mean of 2.1 capillary blood glucose measurements per day, a value clearly insufficient to allow a correct assessment of the efficacy and safety of antihyperglycemic treatment.

In the present study, the median length of stay was 10 days, in accordance to reports from similar populations. Alshabanat et al. that documented a mean length of hospital stay of 10.8 days in 1564 elderly from 5 hospitals in Canada, admitted for exacerbation of COPD [36]. We documented a longer length of stay among patients with heavy alcohol consumption (11.5 vs 10 days, p < 0.05) and nosocomial infections (21 vs 10 days, p < 0.05). Diabetes is a recognized risk factor for nosocomial infections and hospital acquired infections are frequently associated with higher mortality, length of stay and costs [37,38].

The length of stay was negatively correlated with the mean glucose level (r^2 -0.147; p < 0.05), which is in agreement with data from other series that documented an increase in length of hospitalization associated with intensive glycemic control [34].

On the other hand, the glycemic variability seems to have a negative impact on the outcomes of admitted diabetic patients. A retrospective study examined 4262 hospital admissions over a 2-year period the results of the adjusted analysis indicated that for each increase of 10 percentage points in the coefficient of variation, the length of hospital stay increased by 9.7% [39] and, in the present study we documented a positive correlation between the coefficient of variation and the length of stay (p 0.162; p < 0.05).

5. Conclusion

This study confirmed the negative impact of the glycemic variability in the outcomes of diabetic patients admitted with pneumonia and/or acute exacerbation of chronic obstructive pulmonary disease. We also observed a poor glycemic control in patients hospitalized for acute illness. The reinforcement of strategies of high-quality hospital care for diabetes may improve outcomes.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.08.028.

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