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Original Article

Hypoglycemia- simplifying the ways to predict an old problem in the general ward

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ABSTRACT

Objective: To examine the association between hypoglycemic events and inpatient and outpatient mortality rates, and to characterize the profile of patients with diabetes who develop hypoglycemia during hospitalization in order to identify risk factors and potentially avoid it.

Research design and methods: This retrospective cohort study analyzed data of 3410 patients with diabetes hospitalized during 2012. The associations among biochemical measures, severity of hypoglycemia, inpatient length of stay, and mortality during hospitalization, one month and within one year after discharge were evaluated.

Results: Hypoglycemia was observed in 18.5% (633/3410) of patients with diabetes, 83% (529/633) with mild/moderate hypoglycemic values. Adjusted for age and sex, the 30-day mortality rate after discharge was higher in the group with mild/moderate hypoglycemia (HR = 1.749, CI 1.288–2.374, $p < 0.001$) and in the group with severe hypoglycemia (HR = 3.390, CI 2.332–6.100, $p < 0.001$). The mortality rate at the one-year follow-up was higher in the group with mild/moderate hypoglycemia (HR = 1.749, CI 1.288–2.374, $p < 0.001$) and in the group with severe hypoglycemia (HR = 3.390, CI 2.332–6.100, $p < 0.001$).

In multivariate analysis, hemoglobin and albumin below normal values, and creatinine values above the upper limit were strongly associated with hypoglycemia (OR 1.35, 95%CI 1.1–1.6, $p < 0.03$; OR 1.6, 95%CI 1.33–1.89, $p < 0.001$; OR 1.3, 95%CI 1.08–1.55, $p < 0.04$, respectively).

Conclusions: Hospitalized patients with diabetes and low hemoglobin, low albumin or high creatinine levels are at increased risk of developing significant hypoglycemia. Identifying accurate high-risk factors in order to intervene early and efficiently can prevent life-threatening complications.

1. Introduction

Controlling hyperglycemia in hospitalized patients has become an important target for patients with diabetes [1]. For hospitalized patients with diabetes, blood sugar is often unstable, with episodes of hyperglycemia and hypoglycemia. This glucose instability is often attributed to stress, acute illness, surgery, changes in dietary intake and physical activity, and frequent disruption of the patient's regular anti-hyperglycemic regimen [2]. Controlling hyperglycemia in hospitalized patients with diabetes can exacerbate hypoglycemia, especially if tight glucose control is sought [3–5]. Even if tight glucose control is not a goal during hospitalization, frequent episodes of hypoglycemia can occur due to factors such as lack of coordination between food intake and the use of anti-diabetes drugs.

The effect of episodes of hypoglycemia in patients with diabetes was documented in previous studies. It is associated with prolonged hospitalization and is related to higher mortality rates both during and after admission [6]. Moreover, hypoglycemia, as well as hyperglycemia has been associated with approximately twice the risk of cardiovascular disease, suggesting that avoiding severe hypoglycemia may be important to prevent cardiovascular disease in people with type 2 diabetes [7]. General risk factors related to hypoglycemia in patients with diabetes include older age, type 1 diabetes, longer duration of disease and treatment with long-and short acting insulin [8].

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The aim of the present study was to better characterize patients with diabetes who are prone to develop hypoglycemia during hospitalization, using clinical and laboratory parameters to identify preventable risk factors, and to examine the association between hypoglycemic events with inpatient and outpatient mortality rates at different points in time.

2. Methods

2.1. Patients and study design

This retrospective, observational, cohort study consisted of all patients with diabetes who were hospitalized at Wolfson Medical Center, a 700-bed, public, university-affiliated hospital, in 2012. Patients with diabetes were identified through discharge diagnosis codes or by codes for anti-hyperglycemic medications in the electronic hospital pharmacy registry. Patients with diabetes were included only for the first hospitalization in the reference year. Pregnant women, children and patients for whom point of care blood glucose results were not available were excluded.

Patient demographics, dates of admission and discharge were obtained from the electronic medical records. Biochemical data and outcome measures were compared between the study group (patients with diabetes and documented hypoglycemia) and the control group (patients with diabetes, without documented hypoglycemia). The study was approved by the local ethics committee.

2.2. Blood glucose measurements

Blood glucose was extracted using AUTOLIMS, a program that includes all biochemical data. Point of care blood glucose levels were integrated using the institutional blood glucose monitoring system (IGMS). The IGMS consists of a point-of-care, automated glucometer (Accu-Chek Inform, Roche Diagnostics, Indianapolis, IN) and an interactive database. The automated glucometer is located in every inpatient department. Data are transmitted and downloaded automatically to the central hospital Biochemistry Laboratory database. The information system (Roche Cobas IT 1000, Roche Diagnostics, Indianapolis, IN, USA) permits authorized personnel to access, monitor, and analyze data, which can be downloaded to assess temporal trends and identify out-of-range values [9].

2.3. Exposure and outcome measures

Hypoglycemia was defined as blood glucose ≤70 mg/dl. It was further divided into mild-to-moderate hypoglycemia (blood glucose 50–70 mg/dl) and severe hypoglycemia (blood glucose < 50 mg/dl). If the patient had several hypoglycemic events during the same admission, the most severe event was addressed. Laboratory parameters were recorded, including levels of hemoglobin, glycated hemoglobin (when available), albumin, creatinine, cholesterol and c-reactive protein (CRP).

Length of stay was measured by the number of days hospitalized. Mortality was examined during hospitalization, and one month and up to one-year after the index hospitalization.

2.4. Statistical analysis

The data were obtained from the database in Excel files. IBM-SPSS software version 22 was used for statistical analysis. Categorical variables were presented as frequencies and continuous variables as means, standard deviations, medians, and 25th and 75th percentiles. Biochemical data were also grouped according to generally accepted medical indices. The relation between factors were tested with Cox regression models. Multivariate models were built which included all factors that were significant in the univariable models (standardized for patient age). Results are shown as hazard ratios (HR), 95% confidence intervals and statistical significance (p).

Cox models were also used to examine the relationship between hypoglycemia and mortality during hospitalization, mortality within thirty days of hospitalization and mortality within one year of hospitalization. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Hypoglycemia in patients with diabetes during hospitalization

The study sample included 5799 patients with diabetes. Among them, 1606 were readmitted and were excluded according to the inclusion criteria. There were no glucose results for 568 and the discharge departments could not be found for 215. The final study sample included 3410 eligible patients with diabetes. Hypoglycemia was observed in 18.5% (633/3410) of patients with diabetes during hospitalization, 83% (529/633) with mild to moderate hypoglycemic values. Severe hypoglycemia (< 50 mg/dl) was documented in 17% (104/633). The average age of patients with diabetes was 77.11 years. Patients who had hypoglycemia were about 3 years older than patients who did not experience a hypoglycemic event (74.3 versus 71.7 years). Gender distribution was similar: 1681 (49.30%) women and 1729 men (50.70%), but more women had severe hypoglycemia (glucose < 50 mg/dl) 58.65% compared to 41.35% of men (Table 1).

Among the study patients, 2833 (83.1%) were hospitalized in general ward departments, 450 (13.2%) in surgical departments and 127 (3.7%) were in the general intensive care unit. The ratio among departments was similar in terms of hypoglycemic events, of which approximately 87% occurred in the general ward.

3.2. Hypoglycemia and length of hospitalization

The average length of stay of patients who had severe hypoglycemia was more than twice that of patients who had mild to moderate hypoglycemia (11.8 vs. 5.8 days; Table 1).

Table 1
Distribution of hypoglycemia and length of hospitalization.

Parameter	Total	No hypoglycemia	Hypoglycemia overall (≤70 mg/dl)	Mild to moderate hypoglycemia (50–70 mg/dl)	Severe hypoglycemia (< 50 mg/dl)
Number of patients	3410	2777	633	529	104
Age (years)	77.11	71.68	74.32		
Male/female	1419/1681	1419/1358	310/323	267/262	43/61
Hospitalized in internal medicine	2833	2280	553	462	91
Hospitalization in surgical department	450	397	53	43	10
Hospitalization in ICU	127	100	27	24	3
Length of hospitalization (days)					
Mean ± SD	7.23 ± 10.53	5.79 ± 6.63	13.55 ± 18.86	13.89 ± 18.89	11.79 ± 18.7

Table 2
Laboratory values of patients with and without hypoglycemia.[a]

Parameter	Total[a]	Hypoglycemia			
		None	Overall	Mild to moderate	Severe
		> 70 mg/dl	≤70 mg/dl	50–70 mg/dl	< 50 mg/dl
Number of patients	3410	2777	633	529	104
Albumin (g/dl)	3.62 ± 0.53	3.68 ± 0.5	3.37 ± 0.56	3.38 ± 0.56	3.32 ± 0.6
Cholesterol (mg/dl)	163 ± 51	165 ± 51	153 ± 47	152 ± 47	159 ± 45
Creatinine (mg/dl)	1.35	1.29	1.59	1.58	1.63
CRP (mg/dl)	7.01 ± 9.06	6.37 ± 8.73	9.06 ± 9.76	9.28 ± 9.82	7.77 ± 9.43
HBA1C (%)	8.18	8.36	7.55	7.60	7.35
Hemoglobin (g/dl)	11.84 ± 2.1	12.03 ± 2.04	11.05 ± 2.15	11.11 ± 2.08	10.76 ± 2.44
Mean glucose (mg/dl)	173.30 ± 54.89	175.02 ± 56.44	165.75 ± 46.78	166.30 ± 46.66	162.92 ± 47.54

[a] All values are mean + SD.

3.3. Hypoglycemia and biochemical parameters

Table 2 shows the biochemical parameters between groups. In univariate analysis, a significant association was found between hemoglobin levels and hypoglycemic episodes (HR 0.885, CI 0.855–0.915, p < 0.001). Other factors with statistically significant associations were age (HR 1.008, CI 1.002–1.015, p = 0.015), albumin (HR 0.623, CI 0.539–0.718, p < 0.001) and creatinine (HR 1.074, CI 1.026–1.125, p = 0.002). No correlations were found between HbA1c (HR 0.999, CI 0.989–1.009, p = 0.8), CRP or cholesterol and inpatient hypoglycemia.

In multivariate analysis, a significant correlation was found between the following biochemical parameters and the incidence of hypoglycemia during hospitalization: hemoglobin below normal (12 g/dl for women, 14 g/dl for men) (HR 1.623 CI, 1.346–1.958, p < 0.001), albuminemia below 3.5 g/dl (HR 1.749, CI 1.478–2.070, p < 0.001) and creatinine levels above 1.3 mg/dl (HR 1.097, CI 1.286–1.800, p < 0.001). No correlation was found between CRP, cholesterol or HbA1c levels and rate of hypoglycemia (Table 3).

3.4. Hypoglycemia and in-patient department

Hypoglycemic events were relatively less frequent in the surgical departments as compared to general ward departments (HR 0.592, CI 0.446–0.785, p < 0.001). No correlation was found between intensive care units and general ward departments.

Table 3
Risk factors for hypoglycemia among in-patients (Cox regression).

Variable	Hazard ratio	95% Confidence interval	P-value
Hemoglobin below normal value	1.623	1.346–1.958	< 0.001
Hemoglobin above normal value[a]	0.436	0.139–1.369	0.155
Albumin < 3.5 g/dl	1.749	1.478–2.070	< 0.001
Creatinine < 0.7 mg/dl	1.097	0.627–1.918	0.746
Creatinine > 1.3 mg/dl	1.522	1.286–1.800	< 0.001
Cholesterol < 150 mg/dl	1.108	0.909–1.350	0.311
Cholesterol > 199 mg/dl	0.862	0.653–1.138	0.295
HBA1C (%) (normal 4.7–8.5%)			
< 6.5%	1.179	0.830–1.676	0.357
6.5–6.9%	1.115	0.796–1.561	0.527
7–7.9%	1.478	1.021–2.138	0.038
8–8.9%	1.213	0.792–1.859	0.375
9–9.9%	1.747	1.007–3.032	0.047
≥10%	1.625	0.998–2.644	0.051
CRP > 0.5 mg/dl	1.099	0.796–1.517	0.565

[a] Hemoglobin g/dl - normal values for men 14–17 g/dl, normal values for women12–16 g/dl.

3.5. Hypoglycemia, biochemical parameters and hospital department

Multivariate analyses between biochemical measures and hospitalization data (only those significant in previous analyses) for inpatient hypoglycemia indicated that even when we adjusted for the department where the patient stayed, biochemical indicators remained statistically significant (Table 4).

3.6. Hypoglycemia and patient mortality

3.6.1. In-hospital patient mortality

A total of 206 patients died while hospitalized. Of these, 128/2777 (4.6%) had no hypoglycemic events and 78/633 (12.3%) did. Among these, 19/104 (18.3%) patients in the severe hypoglycemia group died. After adjusting for sex and age, no difference in mortality rate was found between patients who experienced hypoglycemic events compared to those who did no.

3.7. Patient mortality rate within 30 days after discharge

Within 30 days of discharge, 231 patients died, representing 6.8% of study patients: 151/2777 (5.4%) without hypoglycemia and 80/633 (12.6%) with hypoglycemia. Among those with severe hypoglycemia, 23 patients died, representing 22% of all patients with severe hypoglycemia. Adjusted for age and sex, the incidence of mortality was significantly higher in the group with mild to moderate hypoglycemia (HR = 1.749, CI 1.288–2.374, p < 0.001) and in the group with severe hypoglycemia (HR = 3.390, CI 2.332–6.100, p < 0.001).

3.8. Patient mortality rate within a year after discharge

A total of 688 patients died within one year after discharge. There were 457/2777 (16.5%) with no hypoglycemia and 231/633 (36.5%) from the hypoglycemia group, including 43 patients who had severe

Table 4
Risk-factors for hypoglycemia among in-patients, adjusted for age and department.

Variable	Hazard ratio	95% Confidence interval	P-value
Age	0.999	0.992–1.006	0.816
Hemoglobin below normal value[a]	1.351	1.107–1.650	0.003
Albumin < 3/5 g/dl	1.592	1.338–1.894	< 0.001
Creatinine > 1.3 mg/dl	1.297	1.086–1.550	0.004
Surgical department	0.616	0.437–0.868	0.006
ICU	0.883	0.584–1.335	0.554

[a] Hemoglobin g/dl - normal values for men 14–17 g/dl, normal values for women 12–16 g/dl.

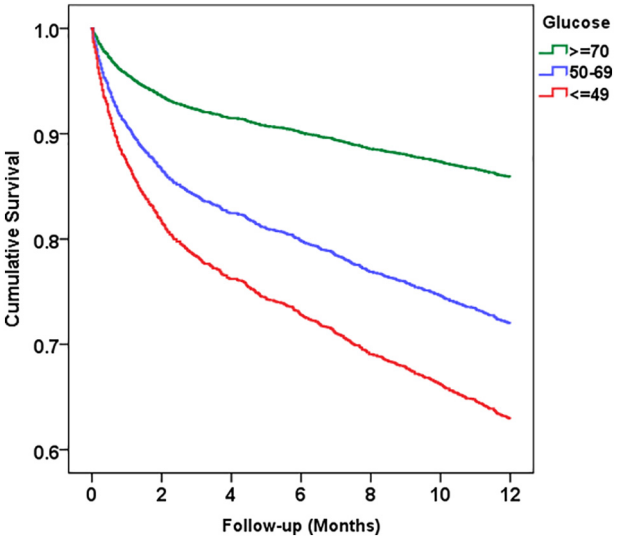

Fig. 1. Hypoglycemia during admission as a risk factor for death over time.

hypoglycemia; representing 41% of all patients in this subgroup. Adjusted for age and sex, the incidence of mortality was significantly higher in the group with mild to moderate hypoglycemia (HR = 1.749, CI 1.288–2.374, $p < 0.001$) and in the group with severe hypoglycemia (HR = 3.390, CI 2.332–6.100, $p < 0.001$) (Fig. 1).

4. Discussion

This retrospective cohort study focused on patients with diabetes who were admitted to a general hospital. Patients with diabetes who experienced hypoglycemia had poorer scores on established outcome measures as compared to those without hypoglycemia in terms of mortality and length of stay. The average length of stay of patients who had hypoglycemia was more than twice that of patients who did not, regardless of its severity. Mortality within 30 days after discharge and within one year of follow-up was significantly higher among patients with diabetes who experienced a hypoglycemic event during hospitalization as compared to those who did not. The correlation between mortality rate and the severity of the hypoglycemia was even stronger.

The average length of stay of patients who experienced hypoglycemia was more than twice that of patients who did not have hypoglycemia. This observation has several possible explanations. Hypoglycemic events may require adjustment of anti-hyperglycemic therapy, causing delays in procedures and tests, which can prolong the hospital stay. Hypoglycemia can also lead to falls, seizures and cardiovascular events that can extend hospitalization. In addition, patients who experience a hypoglycemic event tend to be those who are more ill and require more hospital support, which can all prolong their admission [10,11].

In the current study, hypoglycemia was not associated with a higher in-hospital mortality rate. This finding contrasts with other studies [6,10–12]. However, it can be explained by the shorter hospitalization or the implementation of a quality control program, which improved care for patients with diabetes during hospitalization, and consequently, the in-hospital mortality rate [9]. Another possible explanation for this observation is that detection and treating hypoglycemia are effective in hospital setting and as such prevents its complications, as an increased mortality during hospitalization.

In contrast to in-hospital mortality rate, the 30-day mortality rate after discharge and within one-year of follow-up among patients who experienced hypoglycemia during hospitalization was significantly higher as compared to patients who did not. This finding is consistent with what is already known in the literature. Although hospitalization does not reflect a patient's natural environment, it is reasonable to assume that those who experience hypoglycemia in the hospital are also exposed to hypoglycemia at home. Whereas in the hospital, detection and treatment are effective, detection and optimal treatment at home are less so, which can explain the higher mortality among patients who experienced hypoglycemia in hospital compared to those who did not. Patients with hypoglycemia during hospitalization are also likely to be sicker and consequently to have a higher mortality rate.

In view of these outcomes, which were also reported in other studies [11,12], we sought to identify the most vulnerable patients who might develop significant hypoglycemia during hospitalization. As mentioned, many factors could account for hypoglycemia in hospitalized patients with diabetes, including older age, previous hypoglycemic events, type 1 diabetes, insulin use and sepsis in general [8]. Other studies have focused on various measures to assess the risk of developing hypoglycemia in hospitalized patients, mostly in the intensive care unit or in specific situations [13,14]. However, information in the literature about patients with diabetes and hypoglycemia hospitalized in general wards is scarce. Clinical parameters such as coronary artery disease, infection, poor renal function and even missing a meal were found to be related to recurrent, severe hypoglycemia and readmission [15,16].

The current study revealed several significant risk factors for a hypoglycemic event during hospitalization. The findings indicate that among patients with diabetes, those with the highest risk of developing hypoglycemia have a metabolic profile of either low hemoglobin, or low albumin or high creatinine levels. These laboratory parameters are simple to measure and hence, help clinicians focus on the patients most vulnerable to developing hypoglycemia. Identifying these features has important clinical relevance for the treatment strategy of these patients, including setting higher blood glucose levels during hospitalization, cautious use of various anti-diabetic drugs, especially long- and short-acting insulin analogues and the need for comprehensive patient education before discharge to improve health outcomes. Patients should be instructed about their medications, look carefully at which medications are prescribed, and instructed to follow-up with their endocrinologist as soon as possible.

This study has several limitations. It included only patients admitted to a single academic hospital, which could limit generalizability. The study was conducted by extracting computerized data. Unfortunately, in 2012 information concerning diabetes treatment during hospitalization was not yet computerized and we could not extract these data accurately due to the large sample size. However, the treatment protocol in the general ward concerning hospitalized patients with diabetes is to treat with long- and short-acting insulin analogues. So we assumed that all or most of our patients basically were treated in the same manner. We used point-of-care blood glucose levels in this study and could not check the duration of the hypoglycemic event, which might be significant. On the other hand, central laboratory glucose levels used in many other studies are typically obtained much less frequently, possibly leading to underestimation of the frequency and severity of hypoglycemia. Finally, the retrospective nature of the study did not allow us to draw conclusions about causal relationships and may have led to a bias if missing data were distributed unevenly with respect to the outcomes analyzed.

The strengths of the study are that it is one of the largest analyses of inpatients with hypoglycemia, encompassing > 3000 patients across several hospital departments. The outcomes described were measured after implementation of a standardized health promotion intervention and include inpatient and outpatient outcomes; thus, helping to focus on high-risk patients.

In summary, our findings portray an accurate and simple profile of patients with diabetes who are at high-risk for developing significant hypoglycemia during hospitalization. Admission to general ward, low hemoglobin, low albumin and high creatinine values predispose to hypoglycemia, and as such to its devastating outcomes. This information can be used to increase staff awareness to promptly identify patients at-risk for hypoglycemia. It enables implementing a personalized

care program for diabetes control during hospitalization, in order to avoid immediate complications and late mortality.

Conflicts of interest

None to declare.

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