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Hypoglycemia and Hyperglycemia in Hospitalized Patients Receiving Insulin

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Abstract

Background: Insulin is commonly prescribed to treat hyperglycemia in the hospital setting, but is associated with a risk of hypoglycemia. The objective of this study was to determine the incidence rate and risk factors for hypoglycemia and hyperglycemia in hospitalized patients receiving insulin.

Method: Retrospective cohort study analysing 58,496 patient-days of insulin exposure from 7780 hospitalizations of 5537 adult subjects at a teaching hospital between July 2009 and June 2011. The incidence rate of hypoglycemia (glycemia ≤ 3.9 mmol/L) and hyperglycemia (glycemia >16.7 mmol/L) were evaluated. Glycemia was measured by point-of-care blood-glucose. The association between risk factors and hypoglycemia/hyperglycemia events was determined using a Cox model.

Results: The incidence rates for days with hypoglycemia were 11.1 per 100 patient-days for subcutaneous (s.c.) insulin and 10.4 per 100 patient-days for continuous intravenous insulin (CII). The incidence rates for days with hyperglycemia were 10.2 and 4.6 per 100 patient-days for s.c. insulin and CII, respectively. Clinically relevant risk factors associated with hypoglycemia for subjects on s.c. insulin were: creatinine clearance ≤ 60 mL/min: adjusted hazard ratio (HR) 1.14 [95% CI: 1.03-1.27]; surgery: HR 1.23 [95% CI: 1.04-1.46]; and diabetes: HR 1.79 [95% CI: 1.44-2.23]. For hyperglycemia, the risk factors were diabetes: HR 5.10 [95% CI: 3.65-7.12]; use of systemic corticosteroids: HR 2.13 [95% CI: 1.90-2.38]; and prescription of scheduled with sliding scale insulin: HR 1.89 [95% CI: 1.62-2.21].

Conclusion: The identified risk factors indicate areas for targeted improvement initiatives for glycemic control and should help reduce the rate of hyperglycemic and hypoglycemic events, thereby decreasing the occurrence of adverse outcomes.

Keywords: Hospital; Insulin; Hypoglycemia; Hyperglycemia; Diabetes

Introduction

The worldwide prevalence of diabetes is predicted to rise from 371 million people in 2012 to 552 million by 2030 [1]. In 2011, the prevalence of diabetes among community-dwelling American adults was of 9%, and 30.8% of them were treated with insulin [2]. In a study at a teaching hospital in the United States, as many as 26% of the patients had a diagnosis of diabetes and 12% had undiagnosed diabetes or hyperglycemia [3]. Insulin is frequently used to treat hyperglycemia in the hospital setting because it controls rapidly changing glucose concentrations in patients with unstable clinical conditions (e.g., acute renal insufficiency) [4-6].

Poor glycemic control represents a major safety issue in hospitalized patients with diabetes [7-9]. Hyperglycemia is associated with increased mortality, a higher likelihood of complications (independent of illness severity), a greater risk of admission to an intensive care unit (ICU), and longer lengths of stay [3,6,10-15]. Severe hypoglycemia can lead to complications such as coma, paresis, convulsions, and encephalopathy [4]. Hypoglycemia is also associated with a higher risk of mortality and longer lengths of stay [6,16,17]. One study estimated the latter to 2.5 additional days for each day with hypoglycemia [6,16].

A study conducted across 575 hospitals in the United States with more than 49 million point-of-care (POC) blood-glucose measurements showed that 32% of the values were above 10 mmol/L in ICU and non-ICU patients combined [18]. Glycemic measurements were lower than 3.9 mmol/L for 6.3% of the values in ICU patients and 5.7% for non-ICU patients [18]. In a study of 1990 hospitalized non-ICU patients with diabetes receiving subcutaneous insulin, the following hypoglycemia risk factors were identified: insulin dosing (≥ 0.6 units/kg/day vs. 0.2 units/kg/day), prescription of sliding scale insulin (SSI), elevated serum creatinine, and a lower hematocrit level [19]. To the best of our knowledge, no study has evaluated risk factors for hyperglycemia among all hospitalized patients treated with insulin, whether they were diabetic or not.

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Both the recent recommendations from the Endocrine Society [6] and from the American Society of Health-System Pharmacists expert panel [20] advocate for the monitoring of inpatient rates of hypoglycemia and hyperglycemia to improve glycemic control in the hospital setting. The purpose of this study was to estimate the incidence rates and determine the risk factors for hypoglycemic and hyperglycemic events in hospitalized patients prescribed insulin.

Method

Study design

A retrospective cohort study was conducted. It included all inpatients who received insulin between July 1, 2009 and June 30, 2011 at the Centre hospitalier universitaire de Sherbrooke, a teaching hospital in the province of Québec (Canada). Subjects had to meet the following inclusion criteria: (1) aged ≥ 18 years; (2) at least one day with an active insulin prescription (subcutaneous (s.c.) or continuous intravenous insulin (CII)), and measurement of at least one POC capillary glucose value. Patients hospitalized on psychiatric wards were excluded because they usually have longer lengths of stay and the purpose of this study was to evaluate glycemic control in the context of acute care.

Data sources

Variables of interest were extracted from a hospital database that includes information from (1) the hospital's electronic health record (EHR), containing information on demographic variables, medications, laboratory results, and surgical protocols; and (2) the Med-Echo database, comprising data on diagnosis related to the hospitalization (International Classification of Diseases-10 or ICD-10).

Measurement of blood glucose

POC capillary glucose values were measured using the Precision Xceed Pro glucometer (Abbott, Princetown, NJ, USA) with automatic transfer of the data to the hospital's EHR. Plasma glucose values (venous samples) were not included in the analysis since they are not as frequently monitored.

Hypoglycemia and hyperglycemia

The primary outcomes were the days with at least one hypoglycemic episode (i.e., glycemia ≤ 3.9 mmol/L) and the days with at least one hyperglycemic episode (i.e., glycemia>16.7 mmol/L) based on POC capillary glucose values only. These cut off values were chosen to allow comparison between our results and those previously published [21-23]. The number of episodes per 100 patient-days was determined.

Exposure to insulin

Exposure to insulin was categorized, per patient-day, according to all insulin regimens prescribed during that day: (1) scheduled s.c. insulin only; (2) SSI only; (3) scheduled s.c. insulin and SSI; and (4) CII with or without s.c. insulin (referred to as CII).

Risk factors for hypoglycemia and hyperglycemia

Secondary objectives include the assessment of potential risk factors for hypoglycemia and hyperglycemia grouped in four categories: demographic variables; concomitant medications; diagnoses; and medical specialty at discharge. A detailed description of the potential risk factors is provided in the online appendix.

Validation sub-study

A sub-study was conducted to assess agreement between the information on variables of interest in the hospital's database and the EHR (gold standard). A sample of 250 values was randomly selected for this validation process. Further details are provided in the online appendix.

Statistical analysis

Descriptive statistics were used to report the characteristics of patients and hospitalizations. The incidence rates of days with hypoglycemia (glycemia ≤ 3.9 mmol/L) and hyperglycemia (glycemia >16.7 mmol/L) were estimated. We also assessed the association between selected risk factors and these outcomes. Crude and adjusted HRs were estimated using the counting process model, an extended Cox model, that allows discontinuous time intervals between repeated outcomes, and a correlation structure at the hospitalization level [24]. Separate Cox models were used to examine time to hypoglycemia and hyperglycemia events in the s.c. insulin subgroup and the CII subgroup. We excluded days when POC capillary glucose values were less than 10 mmol/L and SSI was the only insulin prescribed, since patients were unlikely to receive insulin on those days. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Ethics approval

This study was approved by the institution's Ethics Committee.

Results

The cohort was composed of 5,537 subjects who experienced a total of 7,899 hospitalizations. Overall, there were 58,496 patient-days during which insulin was prescribed and at least one POC capillary glucose measurement was available (Figure 1). Table 1 presents patient characteristics per hospitalization and patient-days. The mean age was 67.6 years (SD: 14.1 years), with men accounting for 58.9% of the hospitalizations. In 75.3% of the hospitalizations, subjects were considered to have diabetes, mostly based on a documented diagnosis of diabetes (71.8%). Regarding the type of insulin regimen prescribed, SSI was the most common, representing 32.7% of the patient-days. The overall incidence rates of days with hypoglycemia and hyperglycemia were 10.9 and 8.8 per 100 patient-days, respectively.

Exposure to s.c. insulin

There were 43,739 patient-days with exposure to s.c. insulin alone (without CII exposure). The crude incidence rates of days with hypoglycemia and hyperglycemia events were 11.1 and 10.2 events per 100 patient-days, respectively. Insulin was the only antihyperglycemic medication prescribed on 61.0% of the patient-days. Insulin was prescribed in combination with one, two, or more than two antihyperglycemic agents in 26.4%, 10.9% and 1.7% of the patient-days, respectively.

Exposure to one antihyperglycemic agent, in combination with insulin, was associated with a 24% increase in the risk of experiencing hypoglycemia (HR: 1.24; 95% CI: 1.11-1.38) compared to insulin alone. Exposure to insulin and two antihyperglycemic agents increased the risk by 92% (HR: 1.92; 95% CI: 1.67-2.21) compared to insulin alone. Finally, exposure to more than two antihyperglycemic agents in combination with insulin more than doubled the risk (HR: 2.12; 95% CI: 1.52-2.97) compared to insulin alone.

The mean number of POC capillary glucose measurements per

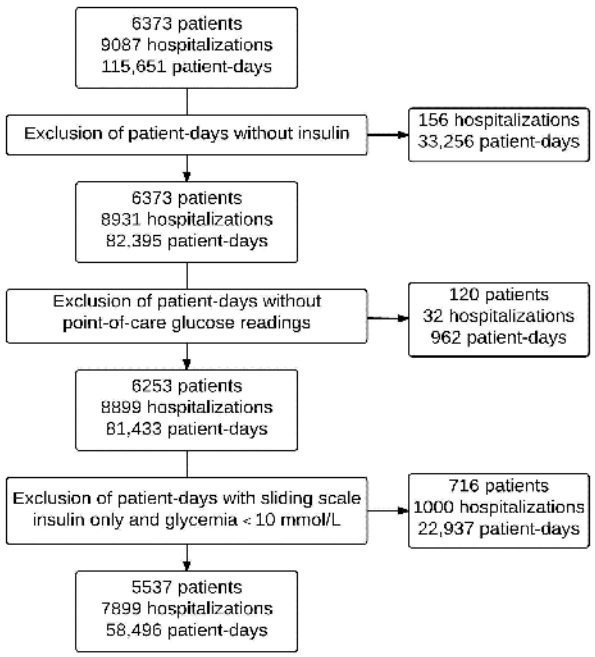

Figure 1: Cohort selection.

patient–day was 3.99 (SD: 1.0) for SSI only; 4.12 (SD: 1.6) for scheduled insulin only; and 4.39 (SD: 1.4) for scheduled insulin and SSI.

Table 2 provides the incidence rates as well as the crude and adjusted hazard ratios of days with hypoglycemia and hyperglycemia by risk factors. Subjects older than 45 years had lower risks of hypo- and hyperglycemia compared to 18-45 year-old. Having surgery increased the risk of hypoglycemia, while being in the ICU reduced this risk. Having diabetes significantly increased both the risks of hypo- and hyperglycemia. Lower renal function (eGFR ≤ 60 mL/min) increased the likelihood of hypoglycemia. Prescription of a SSI significantly reduced the risk of hypoglycemia, and was associated with a higher likelihood of hyperglycemia. Metformin was associated with a slightly higher risk of hypoglycemia and a lower risk of hyperglycemia. Use of insulin secretagogues (sulfonylurea or meglitinide) was associated with increased risks of hypo- and hyperglycemia. Finally, use of systemic corticosteroids significantly increased the risk of hyperglycemia.

Exposure to CII

There were 14,757 patient-days with exposure to CII insulin for which the crude incidence rates of days with hypoglycemia and hyperglycemia were 10.4 and 4.6 events per 100 patient-days, respectively.

Table 3 gives the incidence rates as well as the crude and adjusted hazard ratios of days with hypoglycemia and hyperglycemia by risk factor for the patients exposed to CII insulin. Older age was again associated with reduced risks of hypo- and hyperglycemia. Surgery reduced the risk of hypo- and hyperglycemia (while a greater risk of hypoglycemia was found for subjects on s.c. insulin). ICU stay reduced the risk of hyperglycemia (vs. a reduction in the risk of hypoglycemia with s.c. insulin). Diabetes and the use of corticosteroids were also associated with significantly higher risks of hyperglycemia. As seen with patients on s.c. insulin, lower renal function increased both risks of hypo- and hyperglycemia. Finally, parenteral nutrition was associated with hypoglycemia, which was not observed for patients on s.c. insulin.

Validation sub-study

Results from the validation substudy (Table A.1 of the online appendix) show an agreement ranging from 98.6% to 100% when

	Hospitalizations (n=7899)*	Patient–days (n=58,496)*
Age (years)		
18–44	535 (6.8)	-
45–54	710 (9.0)	-
55–64	1,720 (21.8)	-
65–74	2,437 (30.9)	-
≥75	2,497 (31.6)	-
Men	4,649 (58.9)	-
Weight, kg, Mean (SD)†	82.0 (21.9)	-
Hospitalization length (days)	9 (5–16)	-
Median (Q25–Q75)		
Patient–days with insulin and glycemia values	4 (2–9)	-
Median (Q25–Q75)		
Medical specialty at discharge		
Medical	3,680 (46.6)	-
Surgical	3,200 (40.5)	-
Family medicine	788 (10.0)	-
Other	231 (2.9)	-
Surgery	2,960 (37.5)	-
Intensive care unit	2,918‡ (36.9)	13 250 (22.7)
Diabetes	5,949 (75.3)	-
Treated infection	193 (2.4)	1378 (2.4)
Renal disorder		
<30 mL/min	848 (10.7)	9284 (15.9)
30-59 mL/min	1,868 (23.7)	16 561 (28.3)
≥60 mL/min	5,183 (65.6)	32 651 (55.8)
Hepatic disorder	245 (3.1)	-
Insulin regimens		
Scheduled s.c. only	-	8898 (15.2)
Sliding scale only§	-	19 133 (32.7)
Scheduled s.c. and sliding scale	-	15,708 (26.9)
Continuous intravenous insulin	-	14,757 (25.2)
Anti-hyperglycemic other than insulin		
Metformin	2,709 (34.3)	13,765 (23.5)
Sulfonylureas	1,437 (18.2)	7280 (12.5)
Meglitinides	500 (6.3)	3475 (5.9)
Thiazolidinediones	284 (3.6)	1303 (2.2)
Dipeptidyl peptidase-4 inhibitors	135 (1.7)	528 (0.9)
Alpha-glucosidase inhibitors	16 (0.2)	57 (0.1)
Parenteral nutrition	220 (2.8)	2800 (4.8)
Beta-blockers	3,843 (48.7)	27,541 (47.1)
Systemic corticostroids	2,083 (26.4)	14,695 (25.1)

Kg: Kilogram; Q25-Q75: Quartile 25% - Quartile 75%; s.c.: Sub-Cutaneous; SD: Standard Deviation.

*Figures are numbers (percentage) of hospitalizations or patient–days, unless stated otherwise.

†If no weight was available in the hospitalization, the most recent value observed during a hospitalization at our institution in the previous two years was assigned. No weight value was available during or in the two years prior to hospitalization for 442 hospitalizations.

‡Hospitalization

§Excludes days with sliding scale insulin only and POC capillary glucose values ≤ 10 mmol/L.

Table 1: Subjects' characteristics by hospitalization and patient-days.

Variables	Hypoglycemia (glycemia ≤ 3.9 mmol/L)			Hyperglycemia (glycemia >16.7 mmol/L)		
	IR*	Crude HR	Adjusted HR	IR*	Crude HR	Adjusted HR
Age in years ≥ 18–44	16.97	Reference	Reference	14.2	Reference	Reference
45–54	8.97	0.50 (0.38–0.65)	0.43 (0.33–0.54)	11.64	0.80 (0.55–1.15)	0.72 (0.53–0.98)
55–64	10.8	0.61 (0.49–0.76)	0.51 (0.43–0.62)	11.45	0.78 (0.55–1.11)	0.73 (0.54–1.00)
65–74	10.4	0.58 (0.48–0.71)	0.45 (0.38–0.53)	8.88	0.60 (0.43–0.85)	0.56 (0.41–0.75)
>75	11.53	0.64 (0.53–0.79)	0.53 (0.45–0.63)	9.93	0.67 (0.48–0.94)	0.61 (0.45–0.83)
Female vs. male	11.41	1.05 (0.95–1.15)	1.02 (0.93–1.11)	11.22	1.21 (1.07–1.36)	1.16 (1.03–1.30)
Surgery	11.6	1.03 (0.86–1.24)	1.23 (1.04–1.46)	9.37	0.83 (0.67–1.02)	0.97 (0.79–1.20)
Intensive care unit stay	4.32	0.35 (0.29–0.42)	0.54 (0.45–0.65)	9.12	0.85 (0.73–0.98)	1.02 (0.88–1.19)
Diabetes	11.83	2.87 (2.27–3.63)	1.79 (1.44–2.23)	10.96	3.94 (2.84–5.47)	5.10 (3.65–7.12)
Infection	7.02	0.62 (0.40–0.95)	0.74 (0.49–1.11)	9.98	0.98 (0.71–1.35)	0.95 (0.69–1.33)
eGFR, mL/min >60	9.42	Reference	Reference	9.33	Reference	Reference
30–60	12.68	1.36 (1.23–1.51)	1.14 (1.03–1.27)	11.34	1.23 (1.09–1.38)	1.15 (1.00–1.32)
<30	13.64	1.48 (1.32–1.67)	1.18 (1.04–1.34)	10.91	1.20 (1.02–1.40)	1.08 (0.91–1.28)
Hepatic disorder	9.65	0.86 (0.69–1.08)	0.76 (0.61–0.95)	13.57	1.43 (1.13–1.82)	1.25 (0.98–1.61)
Insulin regimen SSI only	5.06	0.28 (0.24–0.31)	0.27 (0.24–0.31)	9.32	1.42 (1.21–1.66)	1.24 (1.05–1.46)
Scheduled s.c. insulin only	16.49	Reference	Reference	6.52	Reference	Reference
Scheduled s.c. insulin and SSI	15.51	0.92 (0.84–1.02)	0.95 (0.87–1.05)	13.4	2.21 (1.88–2.60)	1.89 (1.62–2.21)
Metformin	11.61	1.05 (0.95–1.16)	1.17 (1.05–1.31)	8.78	0.78 (0.68–0.88)	0.67 (0.60–0.76)
Sulfonylurea	12.61	1.15 (1.02–1.30)	1.75 (1.55–1.98)	12.51	1.26 (1.10–1.44)	1.44 (1.26–1.63)
Meglitinides	13.61	1.25 (1.07–1.45)	1.56 (1.33–1.82)	13.28	1.37 (1.12–1.69)	1.37 (1.12–1.69)
Thiazolidinedione	11.61	1.03 (0.81–1.32)	1.00 (0.77–1.30)	13.63	1.34 (0.95–1.91)	1.30 (0.95–1.79)
DPP-4 inhibitor	6.52	0.56 (0.34–0.92)	0.55 (0.33–0.92)	11.09	1.05 (0.62–1.78)	1.01 (0.61–1.68)
Alpha glucosidase inhibitor	5.88	0.49 (0.13–1.80)	0.62 (0.16–2.38)	7.84	0.71 (0.25–1.97)	0.85 (0.34–2.11)
Parenteral nutrition	2.85	0.24 (0.10–0.59)	0.48 (0.21–1.09)	7.93	0.93 (0.57–1.50)	1.39 (0.86–2.26)
Beta-Blockers	12.52	1.31 (1.19–1.44)	1.14 (1.04–1.26)	9.83	0.93 (0.82–1.04)	0.93 (0.83–1.05)
Systemic corticosteroids	8.53	0.69 (0.61–0.78)	0.85 (0.76–0.95)	15.52	1.95 (1.73–2.20)	2.13 (1.90–2.38)

DPP4 inhibitor: Dipeptidyl Peptidase-4 Inhibitor; Egfr: Estimated Glomerular Filtration Rate; HR: Hazard Ratio; IR: Incidence Rate; s.c.: Sub-Cutaneous; SSI: Sliding Scale Insulin

*IR per 100 patients-days

Table 2: Incidence rate and hazard ratios of days with hypoglycemia (glycemia ≤ 3.9 mmol/L) and hyperglycemia (glycemia >16.7 mmol/L) by potential risk factors for subcutaneous insulin use.

Variables	Hypoglycemia (glycemia ≤ 3.9 mmol/L)			Hyperglycemia (glycemia >16.7 mmol/L)		
	IR[a]	Crude HR	Adjusted HR	IR[a]	Crude HR	Adjusted HR
Age in years ≥ 18–44	11.42	Reference	Reference	5.63	Reference	Reference
45–54	9.54	0.82 (0.59–1.15)	0.74 (0.55–1.00)	3.96	0.71 (0.43–1.17)	0.55 (0.36–0.84)
55–64	9.85	0.85 (0.63–1.13)	0.75 (0.57–0.99)	4.65	0.86 (0.55–1.35)	0.60 (0.42–0.86)
65–74	9.73	0.83 (0.62–1.10)	0.70 (0.53–0.92)	4.28	0.78 (0.51–1.21)	0.43 (0.30–0.62)
>75	11.90	1.05 (0.79–1.41)	0.90 (0.68–1.18)	5.14	0.94 (0.61–1.45)	0.49 (0.34–0.70)
Female vs. male	11.31	1.19 (1.04–1.37)	1.19 (1.05–1.36)	5.10	1.15 (0.94–1.41)	1.09 (0.90–1.33)
Surgery	9.33	0.83 (0.73–0.94)	0.86 (0.75–0.97)	3.34	0.45 (0.37–0.56)	0.54 (0.44–0.66)
Intensive care unit stay	10.14	0.90 (0.79–1.03)	0.91 (0.79–1.05)	3.22	0.47 (0.38–0.58)	0.57 (0.46–0.69)
Diabetes	11.10	1.21 (1.06–1.38)	1.11 (0.96–1.29)	7.13	5.01 (3.77–6.64)	3.98 (2.92–5.42)
Infection	13.11	1.25 (0.89–1.75)	1.27 (0.88–1.83)	1.91	0.46 (0.19–1.07)	0.46 (0.18–1.14)
eGFR, mL/min >60	9.30	Reference	Reference	3.13	Reference	Reference
30–60	11.66	1.25 (1.09–1.44)	1.20 (1.04–1.38)	6.94	2.43 (1.98–2.99)	2.31 (1.90–2.80)
<30	13.89	1.48 (1.23–1.77)	1.43 (1.18–1.73)	8.85	3.03 (2.37–3.88)	2.68 (2.11–3.41)
Hepatic disorder	13.61	1.32 (0.95–1.83)	1.33 (0.95–1.87)	7.56	1.67 (1.01–2.78)	1.53 (1.00–2.35)
Parenteral feeding	7.05	0.50 (0.37–0.67)	0.48 (0.36–0.65)	2.53	0.68 (0.40–1.16)	0.83 (0.51–1.35)
Beta-Blockers	10.87	1.08 (0.96–1.23)	1.03 (0.90–1.17)	5.48	1.43 (1.17–1.77)	1.25 (1.03–1.53)
Systemic corticosteroids	10.60	1.00 (0.86–1.17)	0.96 (0.82–1.12)	5.92	1.69 (1.34–2.14)	1.84 (1.47–2.29)

eGFR: Estimated Glomerular Filtration Rate; HR: Hazard Ratio; IR: Incidence Rate

*IR per 100 patients-days.

Table 3: Incidence rate and hazard ratios of days with hypoglycemia (glycemia ≤ 3.9 mmol/L) and hyperglycemia (glycemia >16.7 mmol/L) by potential risk factors for intravenous insulin use.

comparing values from the database to those recorded in the EHR. Of the excluded patient-days with glycemia <10 mmol/L and SSI as the only prescribed insulin, 35.6% of patients were exposed to insulin. Agreement values obtained from the EHR compared to nursing administration sheets ranged from 95.6% to 98.0% for the insulin categories. The agreement was 89.0% for concomitant medications.

Discussion

In our study on hospitalized subjects receiving s.c. insulin, the incidence rate of days with hypoglycemia (11.1 events per 100 patient-days) was in the range previously reported (5.9 to 17.6 events per 100 patient-days), but the incidence rate of days with hyperglycemia (10.2 events per 100 patient-days) was lower than previously reported (14.8 to 22.8 events per 100 patient-days for hyperglycemia) [21-23]. This could be explained by the fact that subjects with hyperglycemia but without a known diagnosis of diabetes at admission were included. SSI only was the insulin regimen most frequently used (32.7% of patient-days). For many physicians, SSI is simpler to prescribe than scheduled s.c. insulin dosage, but recent guidelines on hospital management of hyperglycemia advocate the use of scheduled s.c. insulin over prolonged SSI use, since the latter is associated with worst glycemic control [6].

The assessment of risk factors shows that patients older than 45 years were at lower risk of hypo- and hyperglycemia. This could be explained by the fact that 18-45 year-old were receiving scheduled s.c. insulin (with and without SSI) more frequently than older patients (data not shown). Another explanation might be that younger patients are more likely to have a previous diagnosis of diabetes. Patients with diabetes were at higher risk of hypoglycemia, an association previously documented [25,26]. Surgery was associated with a higher likelihood of hypoglycemia in subjects on s.c. insulin, which could be explained by the lower intake of food and vomiting in the perioperative period. Surgery was, however, associated with lower risks of hypo- and hyperglycemia in subjects on CII. This could be explained by the fact that these subjects were on an insulin protocol for CII and therefore monitored more closely.

An ICU stay was associated with a lower risk of hypoglycemia while on s.c. insulin and a lower risk of hyperglycemia while on CII. This is probably related to the heightened monitoring of patients in the ICU and common use of a standardized CII protocol. Insulin protocols with demonstrated safety and efficacy may result in lower rates of hypoglycemia in critically ill patients [27].

Lower renal function was associated with higher risks of hypoglycemia and hyperglycemia for s.c. insulin and CII. This finding is consistent with other studies in which higher creatinine levels were independently associated with hypoglycemia [19,28,29]. The higher risk of hyperglycemia could be explained by the fact that it is harder to reach glycemic control is these patients, since they experience hypoglycemia more frequently. Moreover, many antihyperglycemic drugs are contraindicated with chronic kidney disease. Change in kidney function might result in accumulation of the drugs leading to hypoglycemia. Change in medication to avoid these issues might result in temporary hyperglycemia.

Patients on SSI had a lower risk of hypoglycemia and a higher risk of hyperglycemia, which is expected since SSI is less effective than scheduled s.c. insulin to control glycemia, while decreasing the risk of hypoglycemia [6]. The association of insulin with metformin increased the risk of hypoglycemia and decreased the risk of hyperglycemia, which may be explained by improvement in insulin sensitivity. The use of secretagogues increased the risk of hypoglycemia in subjects on s.c. insulin, which was expected since these drugs promote the release of insulin. The higher risk of hyperglycemia observed in these patients could be explained by the fact that uncontrolled subjects were more likely prescribed an oral agent in addition to insulin. Patients on corticosteroids were at a higher risk of hyperglycemia (for both CII and s.c. insulin), which is consistent with this treatment's adverse effects. Parenteral nutrition was associated with a lower risk of hypoglycemia in patients on CII possibly due to the constant supply of calories (e.g., dextrose).

Our study has some limitations that should be considered when interpreting the results. We did not take into account the doses of insulin or the doses of other prescribed antihyperglycemic medications. When the subjects were prescribed CII, we could not differentiate between the patient-days with exposure to CII only and the "transition days" during which the subjects were exposed to CII and s.c. insulin. Therefore, the CII days were grouped as exposure to CII with and without s.c. insulin. Data on eGFR was collected during hospitalization, which may be inaccurate in patients with severe illnesses. Glucagon-like peptide-1 medications were not on the hospital formulary at the time of the study and thus, not readily retrievable from the EHR. The validation process indicated that subjects were exposed to insulin in 35.6% of the excluded patient-days with glycemia <10 mmol/L and prescriptions of SSI only. However, the daily amount of insulin given was minimal with an average of 3.9 units and a standard deviation of 2.4 units. This cutoff was based on a review of the SSI prescriptions. The inclusion of a single academic center limits the generalizability of our results, although this academic center consists of two sites with different patient populations and many different specialties prescribing and managing patients with hyperglycemia.

Despite these limitations, this cohort study included a large number of hospitalized (intensive care and other units) patients with and without diabetes receiving insulin (s.c. or CII) and an important number of variables to identify risk factors for hypoglycemia and hyperglycemia. The Cox model takes into account the correlation between the patient-days of a hospitalization and a patient's possible multiple hospitalizations. This study also highlights significant risk factors related to hypoglycemic and hyperglycemic events, which could lead to poorer outcomes. To the best of our knowledge, this is the first study looking at risk factors for hyperglycemia in hospitalized patients receiving insulin. Finally, the analysis structure (data extraction from the hospital's database and analysis with SAS software) put in place for this study can easily be replicated for different time periods, allowing our institution to assess the impact of new measures implemented to improve glycemic control such as a new standard order set for insulin or new directives for nursing on the timing of measurement of POC capillary glucose in relation to meal time.

In conclusion, clinicians should be aware of the risk factors associated with hypoglycemia and hyperglycemia in hospitalized subjects prescribed insulin. The risk factors identified target areas for improvement initiatives in order to reduce the rate of hyperglycemic and hypoglycemic events. The analysis structure put in place in this study will allow our institution to monitor glycemic control on a regular basis.

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