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PREVENTION AND MANAGEMENT OF INSULIN-ASSOCIATED HYPOGLYCEMIA IN HOSPITALIZED PATIENTS

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Abstract

Objective—To determine whether appropriate therapeutic changes in insulin doses are made to prevent and manage insulin-associated hypoglycemic events in non-critically ill hospitalized patients.

Methods—This retrospective study was conducted in hospitalized adults on medical or surgical floors with insulin-associated hypoglycemia, excluding treatment with insulin infusions, insulin pumps, and parenteral nutrition. The first hypoglycemic event after 48 hours of admission was the index event. Over the 1-year study period, a total of 457 insulin-associated hypoglycemic events were included as index events.

Results—An indication for an insulin dose adjustment was identified in 32 and 42% of patients on day –2 and day –1, respectively, before the index hypoglycemic event, of which 35 and 55%, respectively, had an insulin dose reduction 10%. Following the hypoglycemic event, 44% of patients had an insulin dose reduction of 20%. Therapeutic reduction of the total daily insulin dose by 20% was associated with increased odds of normoglycemia and lower odds of hyperglycemia but was not associated with lower odds of recurrent hypoglycemia on the day following the index hypoglycemic event. There was a high prevalence of hypoglycemic risk factors in this population, with kidney disease and nil per os status being the most prevalent contributing factors.

Conclusion—Adherence to the current practice recommendation to reduce insulin doses in patients with borderline hypoglycemia and following overt hypoglycemia was modest. Further

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Author contributions: E.E. and N.M. designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. S.H.G. interpreted the data and critically reviewed and revised the manuscript. N.M. is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the accuracy of the data analysis.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

studies are needed to understand the associated risks and to define appropriate therapeutic changes for insulin treated patients with borderline and overt hypoglycemia.

INTRODUCTION

Hypoglycemia is a common occurrence in the hospital and is linked to poor clinical outcomes (1). In observational studies of hospitalized patients, both spontaneous hypoglycemia (2–4) and insulin-associated hypoglycemia (3) are linked to increased mortality. Considering that one in four hospitalized patients has diabetes (5) and that insulin is the recommended therapy during hospitalization for the majority of these patients, prevention of iatrogenic hypoglycemia is a significant patient safety issue and a major challenge to our healthcare system. Since insulin accounts for the vast majority of hypoglycemic events (6,7), the Joint Commission and the Institute for Safe Medication Practices have designated it a “high-alert” medication (8). In contrast to the intensive care unit (ICU) setting, where insulin adjustments are commonly driven by nurse-managed protocols, insulin titration in the non-ICU setting is prescriber-driven and requires evaluation of a complex set of clinical, laboratory, and pharmacologic parameters. To prevent iatrogenic hypoglycemia, the American Association of Clinical Endocrinologists/American Diabetes Association consensus statement on inpatient glycemic control recommends that the hospital insulin regimen be reassessed for blood glucose (BG) levels below 100 mg/dL (9). Similarly, the Endocrine Society recommends reduction in the total and prandial insulin dose for BG levels between 70 and 100 mg/dL (5).

Therapeutic inertia is a term typically used to describe delay in the intensification of treatment, a phenomenon that has been implicated in suboptimal chronic glycemic control in the ambulatory setting (10,11). In the context of this study, we define therapeutic inertia as failure to reduce insulin doses based on the patient’s glucose patterns and clinical status. Therapeutic inertia in insulin management has been found to be a common cause of iatrogenic hypoglycemia. Elliot et al (13) found that excess insulin accounted for nearly 60% of hypoglycemic events in a general hospital population, and antecedent borderline hypoglycemia (defined in that study as a BG 90 mg/dL) was present in >60% of severe hypoglycemic episodes (BG <40 mg/dL). Another retrospective study found that the frequency of antecedent mild hypoglycemia was nearly 2-fold higher in patients with severe hypoglycemia (14).

The primary objective of this study was to determine adherence to recommended insulin dose reductions in patients with borderline hypoglycemia and in response to overt hypoglycemia. Secondary objectives were to understand the important factors in clinical decision making of providers when adjusting insulin therapy and to determine whether changes in insulin therapy are associated with different glycemic outcomes following a hypoglycemic event. Based on clinical experience, we hypothesized that the prevalence of antecedent borderline hypoglycemia in the 48 hours before a hypoglycemic event would be high and that the rates of adherence to recommended therapeutic reductions in insulin would be low.

METHODS

This retrospective study was conducted at Johns Hopkins Hospital, a 1,059-bed tertiary care center in Baltimore, Maryland, from January 1 to December 31, 2013. Figure 1 summarizes the inclusion criteria. The study population was limited to adults hospitalized on general medical and surgical floors, excluding ICU, pediatrics, obstetrics, and patients treated with insulin infusions, insulin pumps, or parenteral nutrition. The electronic health record was queried to identify hypoglycemic events, defined as a BG <70 mg/dL. We identified 1,630 hypoglycemic events occurring after the first 48 hours of admission. This time restriction was selected because of the possibility that home antidiabetic medications could contribute to hypoglycemia within the first 24 hours of admission and to allow prescribers a sufficient amount of BG data to make meaningful insulin dose changes. Events in which at least one BG reading per day was not available in the clinically relevant time window from -48 to +48 hours after the index event (n = 180) were excluded. Insulin-associated hypoglycemic index events were defined as hypoglycemia occurring within the duration of action of a dose of subcutaneous insulin (i.e., within 24 hours after glargine insulin; 20 hours after Neutral Protamine Hagedorn [NPH] insulin; 5 hours after aspart insulin; and 20 hours after 70/30 NPH/regular insulin). Based on these eligibility criteria, we identified 457 insulin-associated hypoglycemic events from 385 unique patients over the 1-year study period.

Demographics and diagnostic codes were obtained from an administrative database. Risk factors for hypoand hyperglycemia were identified through chart review of provider documentation, laboratory data, and the medication administration record. We identified the presence of the following risk factors for hypo- and hyperglycemia: diabetes type (type 1, type 2, cystic fibrosis-related, and post-pancreatectomy diabetes), any infectious etiology, sepsis/bacteremia, history of solid organ transplant, acute kidney injury (defined using acute kidney injury [AKI] criteria) (14), chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m²), end-stage renal disease (ESRD) (stage 5 chronic kidney disease [CKD] or dialysis), cirrhosis, and use of systemic corticosteroids. Nutritional status was categorized as eating meals/bolus tube feeds, continuous tube feeds, or nil per os (NPO)/clear-liquid diet. Corticosteroid taper was defined as a dose reduction of at least 20% in the 24 hours prior to the hypoglycemic event.

We selected a clinically relevant time window of 48 hours before and 48 hours after the hypoglycemic event for this study. The purpose of including the prehypoglycemia window was to assess changes in insulin therapy (i.e., prevention), and the purpose of including the post-hypoglycemia window was to assess therapeutic responses (i.e., management). We divided this clinically relevant time window as follows: day -2 (-24 to -48 hours before the event), day -1 (-24 hours to time of event), index hypoglycemic event (reference time point 0), day +1 (time of event to 24 hours after), and day +2 (24 to 48 hours after the event). Glucose data from both point-of-care and serum results were collected. Hypoglycemic events were classified as mild (BG 60 to 69 mg/dL), moderate (BG 40 to 59 mg/dL), and severe (BG <40 mg/dL). At our institution, BG testing is recommended with meals and at bedtime for patients eating regular meals and every 4 hours in patients who are NPO or receiving continuous tube feeds. The day-weighted mean BG was calculated as the sum of all BG readings divided by the total number of BG readings on that day.

Our hospital formulary basal insulins include glargine and NPH; nutritional insulin is aspart insulin delivered with meals or every 4 hours for patients on continuous tube feeds; and correctional insulin is aspart insulin, which is administered as a low-, medium-, or high-dose scale. A low-dose scale is recommended for patient's whose insulin total daily dose (TDD) is <40 units, medium dose for TDD 41 to 80 units, and high dose for TDD >80 units. We classified the correctional scale as too high if it exceeded the recommended scale based on the patient's administered insulin TDD. For patients who received NPH/regular 70/30 mix, the daily basal and prandial doses were calculated by multiplying the TDD by 70 and 30%, respectively.

To assess adherence to insulin dose recommendations, we used our institution's insulin algorithms, which are based on current clinical practice recommendations (5) and are provided to prescribers in the form of "pocketcards" (15). For patients with any episode of hypoglycemia (BG <70 mg/dL), we recommend a 20% reduction in the insulin TDD and switching to a less aggressive correctional insulin scale. For patients with premeal BG 70 to 80 mg/dL or premeal BG 81 to 100 mg/dL with any hypoglycemic risk factors (steroid taper, NPO status or poor oral intake, total pancreatectomy, elderly [defined in this study as age >75 years], acute or chronic renal disease, liver disease, and sepsis), we recommend a decrease in the insulin TDD by 10 to 20%. In this study, we considered a satisfactory insulin dose reduction to be a 10% or greater reduction in the insulin TDD in response to antecedent borderline hypoglycemia (i.e., prevention) and 20% or greater in the insulin TDD in response to the actual hypoglycemic event (i.e., management). When the insulin TDD is adjusted, we recommend re-evaluation of the correctional scale based on the new insulin TDD (e.g., a TDD reduction from 57 to 38 units should result in a change in the correctional scale from medium to low dose, based on the criteria described above).

To evaluate the association between glycemic outcomes and insulin dosing patterns, we defined recurrent hypoglycemia as a BG <70 mg/dL occurring within 4 to 24 hours of the index event (day +1). Considering the duration of action of aspart insulin, repeat hypoglycemic readings occurring within 4 hours of the initial event were considered part of the index event. Normoglycemia was defined as a day-weighted mean BG of 70 to 180 mg/dL in the absence of any recurrent hypoglycemia within 4 hours of the index event. Hyperglycemia was defined as a day-weighted mean BG >180 mg/dL.

Statistical Analysis

Descriptive statistics were used to characterize the study population. The Shapiro-Wilk test was used to evaluate normality. For nonnormally distributed continuous variables, medians and interquartile ranges (IQR) are presented. To compare differences in nonnormally distributed paired data across time intervals, the Wilcoxon signed-rank test was used for matched data (e.g., insulin doses before and after index event) and the Wilcoxon rank sum test for nonpaired data (e.g., insulin doses between groups). Three multivariable logistic regression models were used to analyze the association between insulin doses and glycemic outcomes and other potential confounding variables. Model 1 was adjusted for age and diabetes type (insulin-deficient [type 1 diabetes, cystic fibrosis, and total pancreatectomy] and type 2 diabetes/acute hyperglycemia). Model 2 was adjusted for age, diabetes type, and

nutritional status, which was classified as stable NPO status or stable source of nutrition from day –1 to day +1. In addition to the variables in model 2, model 3 adjusted for the service (medical versus surgical) and composite number of the following hypoglycemic risk factors: steroid taper, AKI, CKD, ESRD, cirrhosis, and bacteremia. A 2-sided *P* value of < .05 was considered statistically significant. Stata Statistical Software (release 13; StataCorp LP, College Station, TX) was used for analyses.

RESULTS

Patient Characteristics

The majority of hypoglycemic events were in the mild to moderate category (Table 1). A diagnosis of diabetes was present in 98%, with type 2 diabetes being the most prevalent type (76%), followed by type 1 diabetes (18%), cystic fibrosis–related diabetes (2%), and total pancreatectomy (2%). The most prevalent risk factor was kidney disease, with 29% having AKI, 43% with CKD, and 14% with ESRD. A history of solid organ transplant was present in 13% and cirrhosis in <1% of patients. An acute infectious etiology (e.g., cellulitis, pneumonia) was present in 33% and bacteremia in 35%. Nearly one-third of patients were NPO at any time on the day before the hypoglycemic event, and nearly two-thirds were receiving regular meals, with only a small minority (7%) receiving continuous tube feeds. Although there was a high prevalence of corticosteroid use (29%), only a small number (5%) of patients had a taper in the steroid dose before the hypoglycemic event.

Prevention of Insulin-Associated Hypoglycemia

On day –2 and day –1, 32 and 42% of patients, respectively, met an indication for an insulin dose reduction on the basis of either a BG of 70 to 80 mg/dL or a BG of 81 to 100 mg/dL in the presence of at least one hypoglycemic risk factor (Table 2). Adherence to the recommended insulin dose reduction (10%) for borderline hypoglycemia was observed in 35 and 55% of patients on day –2 and day –1, respectively.

Among patients who had stable NPO status prior to the hypoglycemic event, 36 and 56% met an indication for an insulin dose reduction on days –2 and –1, of which 25 and 53% had an appropriate therapeutic reduction in insulin, respectively. Among patients with a stable source of nutrition, 28 and 35% met an indication for an insulin dose reduction on days –2 and –1, of which 37 and 49% had an appropriate therapeutic reduction in insulin, respectively.

Management of Insulin-Associated Hypoglycemia

In response to overt hypoglycemia, 44% of the patients had the recommended reduction (20%) in total insulin dose (Table 3). There was slightly higher adherence to insulin dose changes in those with stable NPO status compared to those receiving a source of nutrition (47% versus 40%). The median (IQR) percentage change in the total daily insulin dose was –16.4 (–44.4, 5), with slightly greater reduction in those who had stable NPO status compared to those with stable nutrition (–17.7% versus –14.3%). In the overall population and among those with a stable source of nutrition, there was no change in the basal insulin

dose; however, there was a 20% decrease in the basal dose in patients with stable NPO status.

Glycemic Patterns Before and After Index Event

There was significant glycemic variability in the days before and after the index hypoglycemic event (Fig. 2). Antecedent borderline hypoglycemia was observed in 35 and 45% of patients on days -2 and day -1, respectively (Fig. 3). The prevalence of borderline hypoglycemia increased most dramatically among patients with controlled glucose (peak BG <180 mg/dL) from day -2 to day -1 (16 to 26%). There was also a high prevalence of concurrent antecedent hyperglycemia during this time window, with 71 and 61% of patients having a peak BG >180 mg/dL on days -2 and -1, respectively.

Insulin Dosing According to Hypoglycemic Risk Factors

Approximately 45, 20, and 2% of events occurred in the presence of 1, 2, and 3 or more hypoglycemic risk factors, respectively (Table 4). NPO status, age, ESRD, and steroid taper were associated with statistically significant differences in insulin doses compared to events without these risk factors, whereas AKI, CKD, cirrhosis, and bacteremia were not. Patients with at least one hypoglycemic risk factor had lower total and correctional doses but no differences in basal or nutritional doses. On the other hand, patients with at least three hypoglycemic risk factors had lower basal insulin doses but no differences in other insulin components. At our institution, we recommend an insulin TDD of 0.3 units/kg/day for elderly patients, those with renal or liver disease, and total pancreatectomy. Our results suggest that this lower weight-based recommendation was adhered to only for patients with ESRD, whereas patients with AKI and CKD received a TDD similar to the overall population. There was a nonsignificant trend towards lower insulin doses in patients with cirrhosis and pancreatectomy. For patients undergoing a steroid taper, the median TDD was 0.62 units/kg/day, which is commensurate with our institution's recommendation of 0.6 units/kg/day for patients on steroids.

There are several notable observations related to insulin dosing. First, the median TDD overall corresponds to the recommended weight-based dose for the majority of hospitalized patients (0.4 to 0.5 units/kg/day). Second, even among patients with a source of nutrition, there was little to no nutritional insulin prescribed. Instead, a large proportion of the patients were treated with basal insulin in conjunction with correctional insulin, of which half received an excessively high correctional scale. Third, as expected, NPO patients received approximately half the TDD of those with a stable source of nutrition; however, nearly half of the NPO patients also received an excessively high correctional scale.

Glycemic Outcomes Based on Insulin Doses and Therapeutic Changes

There was no association between adherence to the recommendation to reduce insulin doses by 20% and the likelihood of a recurrent hypoglycemic event (Table 5). On the other hand, this was associated with higher odds of normoglycemia (adjusted odds ratio [OR], 1.58; 95% confidence interval [CI], 1.01 to 2.47) and lower odds of hyperglycemia (adjusted OR, 0.48; 95% CI, 0.28 to 0.80).

A total daily insulin dose >1.0 unit/kg/day, which exceeded the 95th percentile in this population, was not associated with greater odds of recurrent hypoglycemia but was associated with a 2.3 times higher unadjusted odds of hyperglycemia. A 20% reduction in the basal dose was associated with lower odds of hyperglycemia (adjusted OR, 0.51; 95% CI, 0.29 to 0.90) but was not associated with normoglycemia or hypoglycemia. A total daily insulin dose of >0.5 units/kg/day was associated with a 2.1-fold increased adjusted odds of hyperglycemia (95% CI, 1.05 to 4.28) and a lower adjusted odds of normoglycemia (OR, 0.49; 95% CI, 0.24 to 0.97).

A basal:TDD ratio >0.6 was associated with higher odds of hypoglycemia (adjusted OR, 2.15; 95% CI, 1.08 to 4.25), higher odds of normoglycemia (adjusted OR, 2.66; 95% CI, 1.68 to 4.20), and lower odds of hyperglycemia (adjusted OR, 0.21; 95% CI, 0.13 to 0.36). We found no association in glycemic outcomes among those patients with inappropriately high versus appropriate correctional scale according to their total daily insulin requirements.

DISCUSSION

Consistent with our hypothesis, a large proportion (~40%) of patients overall met an indication for a change in insulin therapy; however, adherence to preemptive dose reduction recommendations was only observed in about one-third and one-half of patients on day -2 and on day -1 , respectively. Although our hypothesis of a high prevalence of borderline hypoglycemia prior to the index event was confirmed, we were surprised to find an even greater prevalence of hyperglycemia during this time period. Many patients had concomitant hypo- and hyperglycemia prior to the index event, which may have contributed to the high rates of nonadherence to insulin dose reduction recommendations, since prescribers may have been reluctant to reduce insulin doses in the face of sustained hyperglycemia.

Glycemic targets in the hospital are intentionally less aggressive than those in the outpatient setting, given the increased likelihood of co-existent hypoglycemic risk factors and the lack of proven benefit for tight glycemic control during the relatively short course of hospitalization for non-critically ill patients. At our institution, we recommend a premeal BG target of 80 to 139 mg/dL for most patients and 100 to 150 mg/dL for those with hypoglycemic risk factors, although our findings suggest that a premeal BG target of 100 to 139 mg/dL may be a safer recommendation for all insulin-treated patients.

We found that more than half of patients did not have an adequate therapeutic reduction in insulin dose in response to overt hypoglycemia. Contrary to our hypothesis, a reduction of the TDD of 20% following hypoglycemia was not associated with a lower odds of recurrent hypoglycemia on the day following the index event. Rather, this was associated with a higher likelihood of normoglycemia and a lower likelihood of hyperglycemia. This may reflect a reverse causal association, in which patients with hypoglycemia as an outcome are more likely to have normoglycemic BG readings and less likely to have hyperglycemia than those who do not experience hypoglycemia in the first place.

There is currently no clear guidance on how to reduce insulin doses in response to borderline hypoglycemia, but clinical experience suggests that a 10 to 20% reduction in the insulin

TDD is usually sufficient to prevent overt hypoglycemia. Although the median TDD overall was in line with recommended inpatient dosing (~0.5 units/kg/day), patients with AKI and CKD in this study received more insulin than the renal weight-based recommendation of ~0.3 units/kg/day, which may have contributed to hypoglycemia in this subset of patients (5). It is worth noting that in a large retrospective case-control study, an insulin TDD of 0.4 to 0.6 units/kg/day was not associated with a higher odds of hypoglycemia, even after adjustment for creatinine and other factors (16).

We suspect that inappropriate distribution of the insulin TDD, rather than an excessive TDD, was more likely the contributor to hypoglycemia in many of the index cases. Among patients receiving a source of nutrition, nutritional insulin doses were grossly inadequate, which likely accounts for the significant hyperglycemia preceding the hypoglycemic event. In these individuals, an excessive basal or correctional insulin dose, especially during a period of fasting, may have resulted in hypoglycemia. Indeed, among nearly half of the events in this study, patients were prescribed an excessively high correctional insulin scale based on their total daily insulin requirements. Excessive reliance on the “sliding scale” approach, rather than sensible and timely bolus insulin to accompany meals, is common in the hospital setting and has been shown to be inferior to basal-bolus insulin therapy (17,18). Patients who do not receive proper mealtime bolus doses often have subsequent hyperglycemia, which attracts an excessive correction dose, ultimately leading to hypoglycemia. In this regard, excessive correctional insulin may be a downstream consequence of insufficient nutritional insulin. Although we did not observe differences in glycemic outcomes following a hypoglycemic event based on the appropriateness of the correctional scale, this is likely attributable to the study design, which selected for a group of patients already at higher risk for hypoglycemia.

Although “sliding scale” monotherapy has been widely accepted as an ineffective approach to glycemic control in the hospital (18), correctional insulin in combination with basal insulin (“basal-plus”) insulin has been shown to be as effective as a standard basal-bolus insulin regimen in a select population of non-critically ill hospitalized patients (19). Umpierrez et al (19) showed that in patients with low home total daily insulin requirements (< 0.4 units/kg/day) and relatively normal kidney and liver function, a basal-plus regimen resulted in similar glycemic control compared to a basal-bolus regimen, without increased risk of hypoglycemia. While we did not evaluate home total insulin doses in our study population, a large proportion of patients required total daily insulin doses in the hospital significantly greater than 0.4 units/kg/day and continued to have severe hyperglycemia, suggesting that many of these patients may have been receiving higher amounts of home total daily insulin. In addition, many of the patients in our study had advanced CKD. Higher home basal doses and underlying CKD status may explain why there was such a high prevalence of both hyper- and hypoglycemia in our study among patients who were effectively being treated with a “basal-plus” insulin regimen.

Although basal insulin requirements are typically 40 to 50% of the TDD, NPO patients are expected to receive a larger contribution of the TDD in the form of basal insulin. We found that a basal:TDD ratio over 0.6 was associated with recurrent hypoglycemia, even after adjusting for the patient’s nutritional status; however, this ratio was also associated with a

higher likelihood of normoglycemia and a lower likelihood of hyperglycemia. Although these findings might suggest that a basal:TDD ratio over 0.6 is favorable, we caution against making this inference, as this study was restricted to hospitalized adults with insulin-associated hypoglycemia rather than well-controlled insulin-treated patients.

Encouraging the use of a physiologic insulin regimen of basal and prandial insulin may help to reduce the incidence of insulin-associated hypoglycemia. At our institution, educational initiatives in glucose management include lectures, on-line learning modules, and dissemination of “pocketcards” to medical house staff that emphasize the principles of effective inpatient glucose management. In addition, we have computerized decision support tools to assist providers in prescribing a basal-bolus insulin regimen. Our multicomponent interventions have demonstrated a reduction in the incidence of hypoglycemia in the hospital (15); however, these interventions have not had a significant impact on hyperglycemia, and we recognize the need for additional educational efforts to reach a broader group of prescribers in the hospital, including surgical house staff, hospitalists, and advanced practice clinicians.

Despite the high risks associated with insulin therapy, there have been few published studies focusing specifically on insulin-associated hypoglycemia in the hospital. A main strength of this study was a comprehensive review of a large sample size of medical records to identify risk factors for hypoglycemia, which permitted interpretation of insulin dose adjustments based on glycemic patterns and practice recommendations. Our study, however, has some limitations. It was not designed to determine whether insulin changes in response to borderline hypoglycemia are associated with differences in the odds of overt hypoglycemia. Given our eligibility criteria, patients included were hospitalized for a minimum of 72 hours, which may have selected for a “sicker” population at increased risk of hypoglycemia from other causes; however, as the objective of our study was to determine adherence to insulin dose reductions in response to antecedent borderline hypoglycemia, this is not a major limitation. Another limitation was that cases were not evaluable for missed meals or transport off the floor after administration of scheduled insulin, which has been identified as a root cause of hypoglycemia in hospitalized patients (20).

CONCLUSION

In conclusion, we identified a high prevalence of borderline hypoglycemia in the days before insulin-associated hypoglycemia, with only modest adherence to the clinical practice recommendation to re-assess the insulin regimen based on this glycemic pattern. This confirms our suspicion that therapeutic inertia is a likely contributor to insulin-associated hypoglycemic events in hospitalized patients. Furthermore, less than half of patients had an appropriate therapeutic response to overt hypoglycemia. Additional studies are needed to determine what degree of insulin dose reductions are sufficient to prevent overt hypoglycemia without worsening hyperglycemia in hospitalized insulin-treated patients with borderline hypoglycemia.

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Abbreviations

AKI	acute kidney injury
BG	blood glucose
CKD	chronic kidney disease
ESRD	end-stage renal disease
ICU	intensive care unit
NPH	Neutral Protamine Hagedorn
NPO	nil per os
OR	odds ratio
TDD	total daily dose

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Fig. 1.

Study eligibility criteria. *BG* = blood glucose; *ICU* = intensive care unit; *SQ* = subcutaneous.

Fig. 2.

Blood glucose (BG) pattern over study window. Days were defined as 24-hour timeframes back or forward from the index event (rather than calendar days) as follows: day -2 (-24 to -48 hours before the index event), day -1 (-24 hours to time of index event), index hypoglycemic event (reference time point 0), day +1 (time of event to 24 hours after), and day +2 (24 hours to 48 hours after event). For day -2, day -1, day +1, and day +2, the median and interquartile range (IQR) of the day weighted-mean BG (DWMBG) are shown. For the index event, the median and IQR of the single index hypoglycemic BG value is shown. On day -2, day -1, day +1, and day +2, the median (IQR) DWMBG values were 169 (136, 212), 145 (119, 186), 144 (116, 185), and 157 (126, 198) mg/dL, respectively. The DWMBG was derived from a stable number of measured BG readings throughout the study period; the mean $\pm$ SD number of BG measurements in relation to each day were 4 ± 1.2 (day -2), 4 ± 1.0 (day -1), 1 ± 0 (index event), 4 ± 1.1 (day +1), and 4 ± 1.3 (day +2). Closed circles represent outliers.

Fig. 3.
Peak and nadir blood glucose (BG) values antecedent to hypoglycemic event.

Table 1

Characteristics of Insulin-Associated Index Hypoglycemic Events (N = 457) From 385 Unique Patients

Demographics	
Median age, years (IQR)	59 (48, 68)
Sex, male/female (%)	48/52
Median BMI, kg/m ² (IQR)	27.7 (23.1, 32.8)
Number of events (%)	
Race	
Black	228 (50)
White	197 (43)
Other	32 (7)
Service	
Medical	273 (60)
Surgical	184 (40)
Degree of hypoglycemia	
Mild (BG 60–69 mg/dL)	239 (52)
Moderate (BG 40–59 mg/dL) (%)	187 (41)
Severe (BG <40 mg/dL) (%)	31 (7)
Factors affecting glucose homeostasis	
Diabetes type	
No history of diabetes (%)	12 (3)
Type 1 DM (%)	83 (18)
Type 2 DM (%)	346 (76)
Cystic fibrosis–related diabetes (%)	8 (2)
Total pancreatectomy	8 (2)
Any infectious etiology (%)	126 (28)
Bacteremia (%)	33 (7)
History of solid organ transplant (%)	60 (22)
Acute kidney injury (%)	131 (29)
Chronic kidney disease	
Stage 3 (GFR 30–59 mL/min/1.73 m ²) (%)	134 (29)
Stage 4 (GFR 15–29 mL/min/1.73 m ²) (%)	63 (14)
Stage 5 (GFR <15 mL/min/1.73 m ²) (%)	66 (14)
Cirrhosis (%)	4 (<1)
Nutritional Status in 24 hours prior to hypoglycemic event	
NPO or clear liquid diet (%)	143 (31)
Regular meals (%)	281 (62)
Continuous tube feeds (%)	33 (7)
Corticosteroid Exposure within 48 hours prior to event	

Demographics	
Any treatment with systemic corticosteroids (%)	134 (29)
Corticosteroid taper (%)	23 (5)

Abbreviations: BG = blood glucose; BMI = body mass index; DM = diabetes mellitus; GFR = glomerular filtration rate; IQR = interquartile range; NPO = nil per os.

Table 2

Prevention of Insulin-Associated Hypoglycemia

	Indication for insulin dose adjustment (% of events)		Adherence to total daily insulin dose reduction of 10% (% of events)	
Event	Day -2	Day -1	Day -2	Day -1
Stable NPO status	28/77 (36)	43/77 (56)	7/28 (25)	23/43 (53)
Stable source of nutrition	82/288 (28)	101/288 (35)	30/82 (37)	49/101 (49)
All events	144/457 (32)	191/457 (42)	50/144 (35)	105/191 (55)

Abbreviation: NPO = nil per os.

Table 3

Management of Insulin-Associated Hypoglycemia

Variable	All (N = 457 events)	Stable NPO status (n = 77 events)	Stable source of nutrition (n = 288 events)
Adherence to total daily insulin dose reduction of 20% (%)	199/457 (44)	36/77 (47)	116/288 (40)
Median percentage change in total daily insulin dose (IQR)	-16.4 (-44.4, 5)	-17.7 (-60, 10)	-14.3 (-37.4, 3.2)
Median percentage change in total daily basal insulin dose (IQR)	0 (-40, 0)	-20 (-50, 0)	0 (-25, 0)

Abbreviations: IQR = interquartile range; NPO = nil per os.

Table 4

Weight-Based Insulin Doses By Presence Versus Absence of Hypoglycemic Risk Factors

Events	Median (IQR) Insulin Dose on Day -1, units/kg/day			
	TDD ^a	Basal	Nutr	Corr
All (N = 457)	0.45 (0.26, 0.67)	0.26 (0.17, 0.41)	0.00 (0.00, 0.15)	0.06 (0.01, 0.13)
Stable nutrition (n = 288)	0.51 (0.33, 0.71)	0.28 (0.19, 0.43)	0.00 (0.00, 0.20)	0.07 (0.02, 0.15)
Hypo variables (# of events)				
1 Hypo risk factor (n = 123) vs. 0 Hypo risk factors (n = 154)	0.47 (0.25, 0.65) 0.48 (0.33, 0.70)	0.29 (0.18, 0.44) 0.29 (0.18, 0.42)	0.00 (0.00, 0.15) 0.00 (0.00, 0.15)	0.04 (0.01, 0.11)^c 0.08 (0.03, 0.16)
2 Hypo risk factors (n = 180) vs. < 2 Hypo risk factors (n = 277)	0.42 (0.24, 0.64)^c 0.47 (0.31, 0.67)	0.22 (0.15, 0.33) 0.30 (0.18, 0.43)	0.00 (0.00, 0.15) 0.00 (0.00, 0.15)	0.05 (0.01, 0.14) 0.06 (0.01, 0.13)
3 Hypo risk factors (n = 22) vs. < 3 Hypo risk factors (n = 435)	0.45 (0.23, 0.69) 0.45 (0.27, 0.67)	0.23 (0.14, 0.40) 0.26 (0.17, 0.41)	0.00 (0.00, 0.17) 0.00 (0.00, 0.15)	0.06 (0.04, 0.11) 0.05 (0.01, 0.14)
NPO (n = 77) vs. not NPO (n = 380)	0.27 (0.19, 0.44)^d 0.48 (0.31, 0.69)	0.20 (0.15, 0.30)^d 0.28 (0.18, 0.42)	0.00 (0.00, 0.00)^d 0.00 (0.00, 0.18)	0.03 (0.00, 0.12)^d 0.06 (0.02, 0.14)
Age >75 (n = 45) vs. Age ≤ 75 (n = 412)	0.42 (0.20, 0.55)^c 0.45 (0.27, 0.68)	0.22 (0.16, 0.34) 0.26 (0.17, 0.42)	0.00 (0.00, 0.00)^c 0.00 (0.00, 0.16)	0.03 (0.00, 0.11) 0.06 (0.01, 0.14)
AKI (n = 131) vs. no AKI (n = 326)	0.45 (0.22, 0.67) 0.45 (0.28, 0.67)	0.25 (0.17, 0.41) 0.27 (0.17, 0.42)	0.00 (0.00, 0.18) 0.00 (0.00, 0.15)	0.04 (0.01, 0.13) 0.06 (0.01, 0.13)
CKD (n = 197) vs. no CKD (n = 260)	0.42 (0.24, 0.65) 0.47 (0.31, 0.68)	0.25 (0.17, 0.40) 0.27 (0.17, 0.42)	0.00 (0.00, 0.15) 0.00 (0.00, 0.15)	0.04 (0.01, 0.12)^c 0.07 (0.02, 0.15)
ESRD (n = 66) vs. no ESRD (n = 391)	0.36 (0.23, 0.52)^d 0.47 (0.28, 0.68)	0.20 (0.15, 0.30)^c 0.28 (0.18, 0.42)	0.00 (0.00, 0.14) 0.00 (0.00, 0.15)	0.06 (0.02, 0.13) 0.05 (0.01, 0.13)
Cirrhosis (n = 4) vs. no Cirrhosis (n = 453)	0.32 (0.15, 0.54) 0.45 (0.27, 0.67)	0.22 (0.12, 0.30) 0.26 (0.17, 0.41)	0.03 (0.00, 0.06) 0.00 (0.00, 0.15)	0.09 (0.00, 0.21) 0.06 (0.01, 0.13)
Pancreatectomy (n = 8) vs. no Pancreatectomy (n = 449)	0.36 (0.25, 0.42) 0.45 (0.26, 0.67)	0.20 (0.13, 0.31) 0.26 (0.17, 0.42)	0.00 (0.00, 0.09) 0.00 (0.00, 0.15)	0.00 (0.00, 0.08) 0.06 (0.01, 0.13)
Bacteremia (n = 33) vs. no Bacteremia (n = 424)	0.43 (0.23, 0.61) 0.45 (0.27, 0.67)	0.23 (0.16, 0.42) 0.27 (0.17, 0.41)	0.00 (0.00, 0.00) 0.00 (0.00, 0.32)	0.06 (0.00, 0.12) 0.06 (0.01, 0.13)
Steroid Taper (n = 23) vs. no Steroid Taper (n = 111) ^b	0.62 (0.39, 0.95)^c 0.49 (0.32, 0.67)	0.35 (0.22, 0.46) 0.27 (0.17, 0.43)	0.20 (0.00, 0.35) 0.00 (0.00, 0.19)	0.08 (0.01, 0.18) 0.05 (0.01, 0.14)

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease; Corr = correctional; ESRD = end-stage renal disease; Hypo = hypoglycemic; IQR = interquartile range; NPO = nil per os; Nutr = nutritional.

^aThe sum of the basal, nutritional, and correctional doses does not add up to the total daily dose because medians, rather than means, are shown. The zero values of median for nutritional insulin reflects the fact that very few patients received any scheduled nutritional insulin. Bolded values indicate significant differences in insulin doses by presence vs. absence of hypoglycemic variables.

^bAmong patients receiving systemic steroids.

^c $P<.05$.

^d $P<.01$.

Table 5

Association of Glycemic Outcomes and Insulin Doses in Response to Hypoglycemia

Variable	Glycemic outcome	Odds ratio of glycemic outcome (95% CI)			
		Unadjusted	Model 1 ^a	Model 2 ^b	Model 3 ^c
<i>Total daily insulin dose</i>					
20% vs. <20% reduction in TDD	Hypo	1.60 (0.88–2.89)	1.58 (0.87–2.87)	1.28 (0.65–2.51)	1.29 (0.66–2.55)
	Normo	1.84 (1.25–2.73)	1.70 (1.14–2.54)	1.58 (1.01–2.47)	1.56 (0.99–2.44)
	Hyper	0.35 (0.22–0.56)	0.38 (0.24–0.61)	0.47 (0.28–0.79)	0.48 (0.29–0.81)
>1.0 vs. 1.0 units/kg/day	Hypo	0.94 (0.27–3.21)	0.96 (0.27–3.29)	1.55 (0.43–5.59)	1.51 (0.41–5.54)
	Normo	0.47 (0.22–0.99)	0.51 (0.24–1.12)	0.44 (0.18–1.03)	0.49 (0.20–1.17)
	Hyper	2.34 (1.09–5.03)	2.10 (0.95–4.67)	2.00 (0.83–4.80)	1.74 (0.71–4.27)
<i>Total daily basal dose</i>					
20% vs. <20 % reduction in basal insulin dose	Hypo	1.64 (0.91–2.97)	1.68 (0.92–3.06)	1.53 (0.76–3.08)	1.55 (0.77–3.13)
	Normo	1.51 (1.00–2.26)	1.43 (0.94–2.17)	1.34 (0.83–2.17)	1.33 (0.82–2.16)
	Hyper	0.44 (0.27–0.71)	0.45 (0.28–0.74)	0.52 (0.29–0.91)	0.52 (0.29–0.92)
>0.5 vs. 0.5 units/kg/day	Hypo	0.70 (0.24–2.03)	0.70 (0.24–2.04)	1.07 (0.35–3.23)	1.04 (0.34–3.20)
	Normo	0.65 (0.35–1.18)	0.68 (0.37–1.25)	0.49 (0.24–0.97)	0.55 (0.28–1.10)
	Hyper	1.85 (1.00–3.42)	1.79 (0.95–3.39)	2.12 (1.05–4.28)	1.83 (0.89–3.77)
Basal:TDD ratio >0.6 vs. 0.6	Hypo	2.18 (1.11–4.29)	2.15 (1.08–4.25)	1.88 (0.88–4.02)	1.89 (0.88–4.05)
	Normo	3.00 (2.02–4.45)	2.85 (1.91–4.26)	2.41 (1.54–3.76)	2.70 (1.71–4.27)
	Hyper	0.18 (0.11–0.28)	0.19 (0.12–0.30)	0.25 (0.15–0.41)	0.21 (0.12–0.35)
<i>Correctional scale</i>					
<i>Inappropriately high vs. appropriate scale</i>	Hypo	1.21 (0.67–2.18)	1.21 (0.67–2.20)	1.15 (0.59–2.25)	1.16 (0.59–2.28)
	Normo	0.80 (0.55–1.18)	0.78 (0.53–1.16)	0.82 (0.53–1.26)	0.77 (0.49–1.18)
	Hyper	1.21 (0.80–1.83)	1.24 (0.81–1.91)	1.23 (0.76–1.98)	1.34 (0.77–2.33)

Abbreviations: CI = confidence interval; Hyper = hyperglycemia; Hypo = recent hypoglycemia; Normo = normoglycemia; TDD = total daily dose. Significant values ($P<0.05$) bolded.

^a Adjusted for age and diabetes type (insulin-deficient vs. type 2/acute hyperglycemia).

^b Adjusted for age, diabetes type, and nutritional status (stable source of nutrition vs. stable nil per os status).

^cAdjusted for age, diabetes type, nutritional status, service (medical vs. surgical), and composite number of hypoglycemic risk factors (acute kidney injury, chronic kidney disease stages 3 & 4, end-stage renal disease, cirrhosis, bacteremia, steroid taper).

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