

In Brief

We performed a 130-patient case-control study to examine the patient and hospital care risk factors for experiencing a hypoglycemic patient-day, comparing these factors to similar control patients who were not experiencing a hypoglycemic patient-day. We also examined adherence to our hypoglycemia management protocols, documentation of the event, and adjustments to medications and nutritional regimens that occurred in response to the hypoglycemic event. The most powerful risk factors for hypoglycemia were unexpected nutritional interruption, prior hypoglycemia during the hospital stay, and asynchrony of nutrition delivery and insulin administration. Adherence to hypoglycemia management and documentation standards was poor. Here, we outline strategies to focus improvement efforts on adherence to hypoglycemia treatment protocols and proactive management of patients with these key hypoglycemia risk factors.

Iatrogenic Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention

Analysis of Current Practice at an Academic Medical Center With Implications for Improvement Efforts

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Diabetes has become an increasingly common comorbid condition in acute care settings in the United States.^{1,2} Guidelines advocating near-euglycemic targets have been published and widely promoted,^{3,4} but improvement often proves difficult. Hypoglycemia is the most prominent limiting factor in the glycemic management of type 1 and type 2 diabetes.^{5,6} Fear of hypoglycemia often leads to clinical inertia,^{7,8} with attendant nontreatment of potentially harmful hyperglycemia and a reliance on sliding-scale insulin regimens.⁹ This faulty approach persists in spite of randomized trials demonstrating that physiological (basal-bolus) subcutaneous insulin regimens can achieve improved glycemic control without increasing the frequency of hypoglycemic events.¹⁰

Although fear of hypoglycemia remains a barrier to inpatient glycemic control efforts, there is a paradoxically uneven approach to the treatment of iatrogenic hypoglycemia and methods to prevent it. Recent literature highlights poor adherence to hypoglycemia treatment and documentation standards.^{11,12} Failures to adjust anti-hyperglycemic medication appropriately for sudden loss of caloric exposure or to prevent a recurrent hypoglycemic event are common in both nursing and physician staff, and known risk factors for hypoglycemia

are not identified or not acted on.^{11,13,14} Hypoglycemic excursions on medical/surgical wards by methods other than ignoring glycemic control may be preventable as the rule, rather than the exception.¹⁵ More than 40% of patients experiencing one iatrogenic episode go on to suffer from at least one additional distinct hypoglycemic event, and these recurrent events also appear to be largely preventable.^{11,16}

In 2004, our medical center formed a multidisciplinary glycemic control steering committee and developed “glucometrics” to describe insulin use patterns, glycemic control, and hypoglycemia rates on the medical/surgical wards to gauge the impact of our ongoing improvement efforts. The experience at our academic medical center has mirrored several findings in the literature. The proportion of insulin regimens incorporating a basal insulin tripled through the use of standardized insulin order sets and an insulin management protocol.¹⁷ These interventions predictably improved glycemic control. Perhaps more importantly, hypoglycemia actually decreased significantly, demonstrating that a well-implemented subcutaneous insulin management protocol and order set can achieve both of these important diabetes management goals.¹⁸

Although these improvements were rewarding and clinically significant, our glycemic control steering committee and our safe medication practices committee remained concerned about hypoglycemia as an institutional issue. Approximately 9% of our inpatients with point-of-care (POC) glucose monitoring still experience hypoglycemia, and just as in a recent literature report,¹¹ 40% of our patients with hypoglycemia experience at least one recurrent hypoglycemic event. Furthermore, selected reviews of reported hypoglycemia cases raised concerns that adherence to our hypoglycemia protocol was not uniform and that we were missing opportunities to proactively prevent hypoglycemic events.

Studies have identified advanced age, malnutrition, active cancer, end-stage renal disease, liver disease, congestive heart failure, and other patient factors as contributors to hypoglycemia risk.^{19–25} The use of oral agents, failure to adjust diabetes regimens in response to decreases in oral intake, and unexpected deviation from normal hospital routines have been some of the most common iatrogenic factors contributing to hypoglycemia.^{11,13–15} Most of these studies have relied on a case series methodology, however. This makes it difficult to gauge the relative importance of these risk factors, because these same conditions are also common in patients who do not suffer hypoglycemia.

We devised a case-control study to examine the patient and hospital care risk factors for experiencing a hypoglycemic patient-day and to compare these factors to similar control patients who were not experiencing a hypoglycemic patient-day. We also sought to examine the management of a hypoglycemic event in the hospital setting by looking at adherence to hypoglycemia protocols, documentation of the event, and adjustments to medications and nutritional regimens that occurred in response to the hypoglycemic event.

METHODS

Study Population

Our medical center (University of California, San Diego Medical Center [UCSD MC]) is an academic teaching institution in a major metropolitan center with an average daily census of 540 adult patients. The study popula-

tion was derived from inpatients on general medical and surgical units with POC or serum glucose values obtained in the course of their usual care, and all were on inpatient glucose-lowering agents. Patients were identified from a daily report generated from the clinical UCSD MC database between December 2007 and February 2008. Approval from the Internal Review Board and a waiver of individual informed consent was obtained.

Study Design

This was a matched case-control design. A case series of consecutive patients suffering from an iatrogenic hypoglycemic day were compared to controls that did not have hypoglycemia on that same day. Cases were identified via a computer-generated daily report that captured all patients with a POC or serum glucose value ≤ 60 mg/dl.

The inclusion criteria for cases included 1) adults ≥ 18 years of age; 2) a patient on UCSD MC medical, surgical, or orthopedic service (noncritical care); 3) POC or serum glucose value ≤ 60 mg/dl; and 4) an event occurring while on a glucose-lowering agent, and the timing of the event was consistent with an iatrogenic etiology. For patients with more than one hypoglycemic event in a day, the first event recorded was the index event.

All patients who did not have a POC or serum glucose value ≤ 60 mg/dl that same day were also identified in a daily report. Eligible controls selected for the study were randomly chosen from this pool of patients using a Microsoft Excel random number generator “plugin” utility, and all controls were also on glucose-lowering agents.

Controls were matched by similar lengths of stay to cases, to avoid bias regarding the frequency of prior hypoglycemic events. Patients were excluded if they had a hypoglycemia admission diagnosis or a hypoglycemic event within 24 hours after admission and were also excluded if their hypoglycemia was not induced by insulin or an oral anti-hyperglycemic agent prescribed in the hospital. Intensive care, psychiatry, senior behavioral health, and obstetrics units were also excluded to limit the study population to those services that used the subcutaneous insulin protocol.

Data Collection

An electronic and chart audit of patient demographics and possible hypoglycemia risk factors (Table 1) using medical charts and hospital databases was performed 24–48 hours after the hypoglycemic event. Direct nursing staff queries were also used only to clarify chart documentation if needed. Demographic data included sex, date of birth, admit date and time, hospital site, unit, service, attending name, blood glucose value and source (POC or chemistry), result date and time (generating the hospital date and time the event occurred), and admission diagnosis.

Information was then extracted from the administrative database, chart review, or Siemens Pharmacy systems on both cases and controls; this included subjects’ height, weight, BMI, and race; disease states that may affect glycemic control (as defined below); and nutritional intake and medication regimen information.

Diagnoses of type 1 or type 2 diabetes were derived from admission and emergency department documentation. Liver disease was defined as a documented diagnosis of cirrhosis, end-stage liver disease, portal hypertension, or attendant complications (such as ascites or encephalopathy). Kidney disease was defined as a glomerular filtration rate < 30 ml/min or active dialysis, and congestive heart failure was defined by an ejection fraction $< 40\%$ or a documented diagnosis in the admission history and physical.

Medications (outpatient and inpatient) with the potential to affect glucose control were oral hypoglycemic agents, insulin, steroids, and β -blockers. Nutritional status (type of nutrition/diet patients were on at the time of event) data were collected along with the antihyperglycemic regimen. We also collected data on the presence or absence of a prior hypoglycemic day in the current hospitalization and on the presence or absence of potential nutritional interruption or discordance of nutrition with the antihyperglycemic regimen. We placed nutritional interruption/discordance into one of three categories: new NPO status, new documented nausea/emesis or anorexia, or other causes, such as the administration of nutritional insulin out of sync with nutrition or giving an incorrect or extra dose of insulin. These nutritional interruption/discordance parameters had to be documented in the record

Table 1. Univariate (Unadjusted) Comparison of Cases With Hypoglycemia Versus Controls: Demographics of Patients

Variable	All Participants (n = 130)	Cases (n = 65)	Controls (n = 65)	P value†
Mean length of stay (days)	10.3	10.3	10.3	(matched variable)
Median length of stay (days)	8	8	9	
Male sex (n [%])	57 (52%)	28 (43%)	39 (60%)	0.054
Age (years)‡	57 ± 14	58 ± 13	56 ± 15	0.309
Weight (kg)	81.6	73.4	89.7	0.001
BMI (kg/m ²)‡	28.7 ± 9.9	26 ± 7	31 ± 11	0.004
Race (n [%])				
White	50 (38%)	23 (35%)	27 (42%)	0.471
Black	28 (22%)	16 (25%)	12 (18%)	0.393
Hispanic	34 (26%)	13 (20%)	21 (32%)	0.11
Asian	11 (8%)	9 (14%)	2 (3%)	0.027
Other	7 (5%)	4 (6%)	3 (5%)	0.698
Chronic disease states* (n [%])				
Type 1 diabetes	9 (7%)	6 (9%)	3 (5%)	0.492
Type 2 diabetes	89 (68%)	52 (80%)	37 (57%)	0.001
No diabetes history	32 (25%)	7 (11%)	25 (38%)	0.207
Liver disease	14 (11%)	4 (6%)	10 (15%)	0.09
Chronic kidney disease	34 (26%)	23 (35%)	11 (17%)	0.015
Congestive heart failure	34 (26%)	24 (37%)	10 (15%)	0.015
Outpatient medications (n [%])				
Oral hypoglycemic	33 (25%)	13 (20%)	21 (32%)	0.110
Scheduled insulin	71 (55%)	48 (74%)	23 (35%)	0.001
β-Blocker	47 (36%)	26 (40%)	21 (32%)	0.361
Steroid	27 (21%)	15 (23%)	12 (18%)	0.517
Inpatient medications (n [%])				
Oral hypoglycemic	15 (12%)	8 (12%)	7 (11%)	0.784
Scheduled insulin	86 (66%)	53 (81%)	33 (51%)	0.001
β-Blocker	54 (41%)	33 (51%)	21 (32%)	0.033
Steroid	42 (32%)	21 (32%)	21 (32%)	
Nutrition interruption/discordance	49 (38%)	32 (49%)	17 (26%)	0.007
New NPO order status	25 (19%)	13 (20%)	12 (18%)	0.824
New nausea/emesis or anorexia	26 (20%)	18 (28%)	8 (13%)	0.05
Other (see text for definition)	10 (8%)	8 (12%)	2 (3%)	0.05
Prior hypoglycemia during same admission	38 (29%)	33 (51%)	5 (8%)	0.003

‡ Means ± standard deviations

*Chronic disease states = congestive heart failure, kidney disease, liver disease, or diabetes.

†P values were determined using a χ^2 test or the Mann-Whitney U test, as appropriate.

and needed to be present within the 12-hour time period proximal to the index hypoglycemic event.

For every case with a hypoglycemic event, additional information was collected on management of the event and adherence to hypoglycemia treatment protocols: documentation of the hypoglycemic event other than the value itself; any temporary or permanent harm induced by the event; minutes until the next glucose value was checked after event; minutes until resolution (defined as a documented glucose value ≥ 80 mg/dl); amount of carbohydrate given; changes in regimen (i.e., increase in dextrose or nutrition or decrease in hypoglycemic agents); and description of actions taken.

A secure electronic database was maintained to store the patient data.

To determine power, we estimated a medium effect size of 30% difference in nutritional interruption/discordance between cases and controls. A sample size of 49 subjects in each group was needed to achieve power of 0.8 at an $\alpha < 0.05$ using the χ^2 statistic.

Analysis

We used χ^2 analysis to compare the cases and controls by the multiple factors. Initial univariate analyses were examined using a matched logistic model for predicting cases. Variables were then grouped by three categories: 1) disease (diabetes diagnosis, congestive heart failure, liver failure, chronic kidney disease), 2) medications, and 3) demographics, including age, sex, BMI, nutritional interruption/discordance, and prior hypoglycemic day. Based on these three separate analyses, variables that remained robust with a significant value of $P < 0.10$ were entered into a final multivariate model with adjustments for age and sex.

We also looked at adherence to the medical center hypoglycemia treatment protocol, treatment of the event, and changes in the regimen to prevent another occurrence. If the hypoglycemic event did not result from a temporary nutritional interruption/discordance, the patient was judged to remain at risk for future episodes unless the antihyperglycemic regimen was reduced or carbohydrate/nutritional delivery was increased.

RESULTS

Study Population: Characteristics and Univariate Analysis of Cases Versus Controls

There were a total of 65 sequential cases and 65 controls in the study. The demographic and baseline characteristics of both groups with unadjusted univariate comparisons between them are listed in Table 1.

Demographic information

There was a statistically insignificant trend for more males to be controls ($P < 0.054$) and no difference in age between the two groups. Cases had a significantly lower BMI than controls, with an average of 26 ± 17 and 31 ± 11 kg/m², respectively ($P = 0.004$), and had a mean weight 16 kg less than controls. Ethnicity was not significantly different in cases versus controls in the univariate analysis, except that cases were more likely to be Asian than controls (nine Asian cases vs. two Asian controls, $P = 0.027$).

Chronic disease states

Cases had a higher prevalence of chronic kidney disease (23 cases vs. 11 controls, $P = 0.015$) and a higher prevalence of congestive heart failure (24 cases vs. 10 controls, $P = 0.015$). There was no difference in liver disease prevalence between cases and controls. Seventy-five percent of the study population carried a prior diagnosis of diabetes. The diagnosis of type 1 diabetes did not differ significantly between cases and controls, but there were more cases ($n = 52$) than controls ($n = 37$) with type 2 diabetes ($P < 0.004$).

Treatment regimens

Before admission, 71 of 130 (55%) study participants were on scheduled insulin, and 33 (25%) were on oral antihyperglycemic agents. The inpatient medication regimens shifted toward more frequent use of scheduled insulin (86 of 130; 68%) and less use of oral antihyperglycemic regimens (15 of 130; 12%). Cases were more likely than controls to have scheduled insulin as an outpatient (48 cases vs. 23 controls, $P < 0.001$), and this same trend carried through in the inpatient setting, with 81% of the cases on scheduled insulin compared to 51% of the controls ($P < 0.001$). β -Blockers and steroids were both common in outpatient and inpatient settings, and

inpatient β -blockers were more common in cases than controls (51% of cases vs. 32% of controls, $P = 0.033$). We did not detect discontinuation of steroids as an etiology for any hypoglycemic event.

Nutritional interruption/discordance and prior hypoglycemia

New NPO order status was present in 13 cases and 12 controls. New nausea/emesis or anorexia was more common in cases than controls (18 cases vs. 8 controls, $P = 0.05$), as were "other" causes of nutritional/antihyperglycemic discordance (8 cases vs. 2 controls, $P = 0.05$). Nutritional interruption/discordance was present in some form in 49% of hypoglycemia cases vs. 26% of matched controls ($P = 0.007$). Twelve patients experienced more than one source of nutritional interruption/discordance, accounting for the discrepancy in totals of the component parts of this parameter with the composite totals.

Remarkably, more than half of hypoglycemic cases had experienced a prior hypoglycemic day during their inpatient stay, whereas only 8% of matched controls had experienced a prior hypoglycemic day during their inpatient stay (33 cases vs. 5 controls, $P = 0.003$).

Adjusted Analysis of Hypoglycemia Risk Factors

Sub-analysis by the variables grouped within common sets of disease, medication, or demographics identified the variables entered into the final model. The age- and sex-adjusted final multivariate model is shown in Table 2. The presence of a prior hypoglycemic day during the admission was the dominant predictor of a hypoglycemic event, with nutritional interruption/discordance and insulin use as an outpatient also emerging as pertinent factors. Race, BMI, the disease states, and other factors did not add significant predictive ability to these factors.

Management of Event and Adherence to Protocol

Tables 3 and 4 summarize hypoglycemia therapy and regimen adjustment for the 65 patients who had either a POC or chemistry glucose value ≤ 60 mg/dl. Of those 65 patients, 11 (17%) had severe hypoglycemia, classified as a blood glucose ≤ 40 mg/dl. Only 2 of the 65 patients suffered any

Table 2. Final Multivariate Logistic Analysis Pseudo $R^2 = 66\%$, $P < 0.0001$

	Odds Ratio	P value	95% Confidence Interval
Age	1.01	0.881	0.94–1.07
Sex	0.34	0.222	0.06–1.91
Congestive heart failure	6.35	0.111	0.65–61.47
Chronic kidney disease	5.16	0.131	0.61–43.30
Nutritional interruption/discordance	12.09	0.032	1.23–118.05
Prior hypoglycemic day	31.18	0.004	2.91–333.67
Insulin as outpatient	15.57	0.026	1.39–174.80

documented harm. One patient had lethargy and another was tremulous for a brief time beyond glucose value correction, prompting a brief transfer to an intermediate level of care for observation.

The UCSD MC hypoglycemia treatment protocol states that blood glucose has to be checked every 15 minutes after a hypoglycemic event until two consecutive values ≥ 80 mg/dl have been attained. The median time until the next glucose value was checked was 60 minutes, with a range of 8–600 minutes. The median time until documented resolution (with a glucose value of ≥ 80 mg/dl) was 180 minutes with a range of 10–1,260 minutes. Nineteen of the 65 cases (29.2%) of hypoglycemic events were not documented anywhere in the chart or progress notes except for the recording of the low value itself.

As noted above, 32 of the 65 hypoglycemic cases had some form of nutritional interruption or antihyperglycemic/nutritional discordance, leaving 33 who had no such temporary reason for their hypoglycemic event. Of these 33 hypoglycemic cases without temporary nutritional interruption/discordance as a contributing factor, 17 had a reduction in their scheduled insulin dose, 2 had an oral agent discontinued, 4 had their carbohydrate consumption increased, and 10 (30%) had no adjustment made.

DISCUSSION

We sought to evaluate risk factors for iatrogenic hypoglycemia, compare the frequency of these risk factors in a matched control group, and examine the response to iatrogenic hypoglycemic events. Our study has several findings of interest with practical

implications for multidisciplinary improvement teams.

Finding: *The documentation and treatment of iatrogenic hypoglycemia is poor, and adherence to existing hypoglycemia protocols was suboptimal.* There was a very long delay in documented blood glucose monitoring after an event, which clearly deviates from protocol. In 7 of the 65 hypoglycemic cases, the nurse reported that they did not receive proper notification of the hypoglycemic chemistry lab value, leading to long delays in the treatment and subsequent retesting.

Documentation of the hypoglycemic event varied from a detailed description of what the patient's current condition was leading up to the event and exactly how much carbohydrate was given as treatment to merely mentioning a patient's hypoglycemic glucose value. Documentation of the event and treatment was also difficult to retrieve because of inconsistencies in where the documentation was placed (nurses' progress notes vs. with POC glucose tests vs. in the medication administration record). Physician performance was also suboptimal, in that appropriate adjustments to avert repeated episodes of iatrogenic hypoglycemia often did not occur. This poor performance confirms the experience from other studies.^{11,12,14}

Implications: *The mere existence of a complete institutional hypoglycemia protocol provides no assurance that proper care of iatrogenic hypoglycemia is taking place. Monitoring and improving adherence to a hypoglycemia protocol should be a top priority for glycemic control steering committees.* Simplification of hypoglycemia protocols, with a focus on treatment of the event, assessment of

the etiology, notification of the treating clinician, and documentation in a standardized format should be stressed. Improvement efforts must include ongoing assessment of adherence to the hypoglycemia protocol.

Finding: *Unexpected nutritional interruption/discordance is one of the most important risk factors for iatrogenic hypoglycemia.* Our univariate analysis confirmed several risk factors for iatrogenic hypoglycemia (low BMI, congestive heart failure, chronic kidney disease, and β -blockade). The failure to confirm other reported risk factors (advanced age, type 1 diabetes, liver disease) is likely the result of a limited sample size and multiple comparisons, and improvement teams should still consider these conditions as signals to use lower initial doses of insulin.

More importantly, nutritional interruption/discordance and a prior hypoglycemic event were strong predictors of subsequent hypoglycemia in both univariate and adjusted multivariate analyses. There were three categories making up the composite nutritional interruption/discordance parameter: new NPO order status, new documented nausea/emesis or anorexia, and other causes, such as the administration of nutritional insulin out of sync with nutrition or giving an incorrect or extra dose of insulin. The NPO order status was not a risk factor for hypoglycemia in our institution, which incorporates basal/nutritional/correction dose insulin terminology into orders and the medication administration record and standing orders in the care of NPO patients.^{17,18} However, the other two categories of nutritional interruption/discordance were a risk factor at our institution.

Table 3. Treatment of Hypoglycemic Cases

Total hypoglycemia cases (<i>n</i>)	65
Severe hypoglycemia cases (blood glucose ≤ 40 mg/dl) (<i>n</i> [%])	11 (17%)
Permanent harm	0
Temporary harm (<i>n</i> [%])	2 (3%)
Nutritional interruption/discordance risk factor present (<i>n</i> [%])	32 (49%)
Nutritional interruption/discordance risk factor absent (<i>n</i> [%])	33 (51%)
No documentation except glucose value recordings (<i>n</i> [%])	19 (29%)
Minutes elapsed to next recorded value (median [range])	60 (8–600)
Minutes elapsed to resolution (median [range])	180 (10–1,260)

Table 4. Regimen Adjustments in Response to Cases With Hypoglycemia and No Putative Transient Nutritional Interruption/Discordance Etiology

Nutritional interruption/discordance risk factor absent (<i>n</i>)	33
Insulin dose reduced (<i>n</i> [%])	17 (52%)
Oral antihyperglycemic agent decreased/stopped (<i>n</i> [%])	2 (6%)
Carbohydrate supply increased (<i>n</i> [%])	4 (12%)
No adjustment made (<i>n</i> [%])	10 (30%)

Implications: *New nausea/eme-sis or anorexia should trigger more frequent monitoring of glucose and a lower threshold for increasing carbohydrate delivery or reducing the intensity of antihyperglycemic therapy. Nutrition delivery, glucose monitoring, and insulin delivery should be synchronized as much as possible.* Our findings suggest that interruption of nutrition is exceedingly common in inpatients and that staff often do not take action that could avert hypoglycemia in these situations. Although we have made attempts for years to improve the synchronization of nutrition, monitoring, and insulin delivery, many opportunities for improvement remain. Educational efforts should focus on these triggers for added attention and adjustment.

Finding: *One of the strongest predictors of an iatrogenic hypoglycemic event is experiencing a prior hypoglycemic event, and adjustments to avert recurrent hypoglycemia*

are often absent or suboptimal. An impressive 51% of hypoglycemia cases had suffered a prior hypoglycemia event earlier in their hospitalization. Unfortunately, the opportunities to avert repeated episodes are often not realized, and suboptimal or no changes were made in many patients with hypoglycemia (even those without possible temporary mitigating circumstances). This finding has also been seen by others.^{11,13–15}

Implications: *Concurrent scrutiny and proactive adjustment of regimens in patients with iatrogenic hypoglycemia or near hypoglycemia could dramatically reduce iatrogenic hypoglycemia.* As a result of this study, we are planning an interventional strategy for patients approaching or developing hypoglycemia. A daily report of all patients with glucose values in the danger zone (for example, any glucose < 80 mg/dl) will be forwarded to a nurse/hospitalist consultant team. This team will assess the glucose values

and treatment regimen and intervene with focused interventions, such as templated consultation notes and phone calls, with recommendations for changes in either the antihyperglycemia regimen or nutrition plan. Although confirmatory research is needed, we believe this proactive approach looking at concurrent daily glucose values is much more likely to be successful in securing improvement than retrospective review of hypoglycemia cases.

Finding: *Many disciplines influence iatrogenic hypoglycemia.* Surgical, medical, pharmacy, laboratory, dietary, nutritional, and nursing personnel were all involved in the care of these patients, and opportunities for improvement were noted in all of them.

Implications: *Multidisciplinary approaches are needed for multidisciplinary problems.* We have already started educating our hospital staff, including nurses, physicians, pharmacists, dietary services staff, and laboratory staff, about the insulin management and hypoglycemia treatment protocols. Nursing in-service training sessions and skills workshops on proper documentation have been given and will continue throughout the medical center, and educational sessions are taking place for a variety of services. All disciplines will be involved as we measure the impact of revising and simplifying our current hypoglycemia protocol and other educational efforts.

Our study had several limitations. Sample size calculations, while sufficient to look at key variables, may not be sufficient to support a robust analysis of multiple factors. As mentioned previously, documentation of hypoglycemia treatment was often poor, so possible causes of the hypoglycemic event, as well as the exact treatment and changes made to regimens, were subject to the data collectors' search and interpretation. Also, we waited only 48 hours after an index event to collect information on treatments given or adjustments to regimens, which means we may have missed any changes made after 48 hours.

Our study also included patients who did not have a diagnosis of diabetes. There was a trend for having more cases with a diabetes diagnosis than controls. Although this trend did not reach statistical significance, controls were not on scheduled insulin as fre-

quently in the outpatient or inpatient setting, potentially influencing other comparisons.

Still, we think our findings and implications will hold up despite these relative shortcomings because our study also demonstrates several strengths, including rigorous data collection techniques, the presence of a matched control group, and a logistic regression analysis that adjusts for the effect of multiple cofactors.

CONCLUSIONS

Iatrogenic hypoglycemia is pervasive and is the major barrier to achieving improved inpatient glycemic control. The treatment of iatrogenic hypoglycemia is often suboptimal, and improvement efforts should focus on simplifying hypoglycemia protocols and monitoring adherence to institutional standards of treatment, assessment, notification, and documentation of hypoglycemia episodes. Although traditional disease state-related risk factors for hypoglycemia remain important in calculating initial insulin dosages, the more dynamic risk factors of sudden nutritional interruption, mistiming of the antidiabetes regimen with nutritional intake, and prior hypoglycemic events are more important areas on which to focus improvement and prevention efforts.

Multidisciplinary efforts to increase the frequency of monitoring, initiate appropriate adjustment of antihyperglycemic medication, and increase carbohydrate supply in the face of these risk factors should result in significant reductions in iatrogenic hypoglycemia without significant loss of glycemic control. Proactive adjustment of the monitoring and treatment regimens of patients with hypoglycemia or near-hypoglycemia is a strategy worthy of further study and improvement activities.

References

¹Centers for Disease Control and Prevention: Data and trends. 2005 [article online]. Available online from <http://www.cdc.gov/diabetes/statistics>. Accessed 20 August 2008

²American Association of Diabetes Educators: Facts and statistics. 2007 [article online].

Available online from http://www.diabeteseducator.org/export/sites/aade/_resources/pdf/Diabetes_Fact_Sheet.pdf. Accessed 20 August 2008

³Garber AJ, Moghissi ES, Bransome ED Jr, Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, Van den Berghe G, Zamudio V, the American College of Endocrinology Task Force on Inpatient Diabetes Metabolic Control: American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 10:77–82, 2004

⁴American Diabetes Association: Standards of medical care in diabetes—2008 [Position Statement]. *Diabetes Care* 31 (Suppl. 1):S12–S54, 2008

⁵Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002

⁶American College of Endocrinology and American Diabetes Association: American College of Endocrinology/American Diabetes Association consensus statement on inpatient diabetes and glycemic control: a call to action. *Diabetes Care* 29:1955–1962, 2006

⁷Phillips LS, Branch WT, Cook CB, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC, Barnes CS: Clinical inertia. *Ann Intern Med* 135:825–834, 2001

⁸Cook CB, Castro JC, Schmidt RE, Gauthier SM, Whitaker MD, Roust LR, Argueta R, Hull BP, Zimmerman RS: Diabetes care in hospitalized noncritically ill patients: more evidence for clinical inertia and negative therapeutic momentum. *J Hosp Med* 2:203–211, 2007

⁹Umpierrez G, Maynard G: Glycemic chaos (not glycemic control) still the rule for inpatient care: how do we stop the insanity? *J Hosp Med* 1:141–144, 2006

¹⁰Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, Puig A, Mejia R: Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 Trial). *Diabetes Care* 30:2181–2186, 2007

¹¹Varghese P, Gleason V, Sorokin R, Senholzi C, Jabbour S, Gottlieb JE: Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. *J Hosp Med* 2:234–240, 2007

¹²Anthony M: Treatment of hypoglycemia in hospitalized adults. *Diabetes Educ* 33:709–715, 2007

¹³Braithwaite SS, Buie MM, Thompson CL, Baldwin DF, Oertel MD, Robertson BA, Mehrotra HP: Hospital hypoglycemia: not only treatment but also prevention. *Endocr Pract* 10 (Suppl. 2):89–99, 2004

¹⁴Garg R, Bhutani H, Jarry A, Pendergrass M: Provider response to insulin-induced

hypoglycemia in hospitalized patients. *J Hosp Med* 2:258–260, 2007

¹⁵Smith WD, Winterstein AG, Johns T, Rosenberg E, Sauer BC: Causes of hyperglycemia and hypoglycemia in adult inpatients. *Am J Health Syst Pharm* 62:714–719, 2005

¹⁶Braithwaite SS, Michota F: Avoiding complications in the hospitalized patient: the case for tight glycemic control. *J Hosp Med* 2 (Suppl. 1):1–4, 2007

¹⁷Lee J, Clay B, Ziband Z, Clay B, Maynard G: Indication based ordering: a new paradigm for glycemic control in hospitalized inpatients. *J Diabetes Science Tech* 2:349–356, 2008

¹⁸Maynard G, Lee J, Phillips GW, Fink EJ, Renvall M: Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. *J Hosp Med*. In press

¹⁹Briscoe VJ, Davis SN: Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology, and management. *Clin Diabetes* 24:115–121, 2006

²⁰Cryer PE: Current concepts: diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350:2272–2279, 2004

²¹Tomky D: Detection, prevention, and treatment of hypoglycemia in the hospital. *Diabetes Spectrum* 18:39–44, 2005

²²Arem R: Hypoglycemia associated with renal failure. *Endocrinol Metab Clin North Am* 18:103–121, 1989

²³Fischer KF, Lees JA, Newman JH: Hypoglycemia in hospitalized patients: causes and outcomes. *N Engl J Med* 315:1245–1250, 1986

²⁴Chuhwak EK, Pam SD: Diabetes co-existing with chronic liver disease: clinical features and response to therapy. *Niger J Med* 16:156–160, 2007

²⁵Cryer PE, Davis SN, Shamoom H: Hypoglycemia in diabetes. *Diabetes Care* 26:1902–1912, 2003

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