Hypoglycemia and Clinical Outcomes in Patients With Diabetes Hospitalized in the General Ward

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OBJECTIVE — Hypoglycemia is associated with adverse outcomes in mixed populations of patients in intensive care units. It is not known whether the same risks exist for diabetic patients who are less severely ill. In this study, we aimed to determine whether hypoglycemic episodes are associated with higher mortality in diabetic patients hospitalized in the general ward.

RESEARCH DESIGN AND METHODS — This retrospective cohort study analyzed 4,368 admissions of 2,582 patients with diabetes hospitalized in the general ward of a teaching hospital between January 2003 and August 2004. The associations between the number and severity of hypoglycemic (≤50 mg/dl) episodes and inpatient mortality, length of stay (LOS), and mortality within 1 year after discharge were evaluated.

RESULTS — Hypoglycemia was observed in 7.7% of admissions. In multivariable analysis, each additional day with hypoglycemia was associated with an increase of 85.3% in the odds of inpatient death ($P = 0.009$) and 65.8% ($P = 0.0003$) in the odds of death within 1 year from discharge. The odds of inpatient death also rose threefold for every 10 mg/dl decrease in the lowest blood glucose during hospitalization ($P = 0.0058$). LOS increased by 2.5 days for each day with hypoglycemia ($P < 0.0001$).

CONCLUSIONS — Hypoglycemia is common in diabetic patients hospitalized in the general ward. Patients with hypoglycemia have increased LOS and higher mortality both during and after admission. Measures should be undertaken to decrease the frequency of hypoglycemia in this high-risk patient population.

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In recent years, there has been an increasing focus on controlling hyperglycemia in hospitalized patients (1). Hyperglycemia is associated with adverse clinical outcomes, and randomized controlled trials in intensive care units (ICUs) have shown that aggressive treatment of elevated blood glucose improves outcomes. Tight glucose control, however, is not without risk. Studies have suggested that the benefits of tight glycemic control may be at least partially offset by the increased risk of hypoglycemia (2,3). In particular, hypoglycemia in ICUs has been linked to increased risk of mortality, seizures, and coma (4).

It remains unknown whether the risks associated with hypoglycemia found in critically ill patients can be generalized to non-ICU settings. The etiology of hypoglycemia in ICU patients may be different from that in patients hospitalized in the general ward. A number of risk factors for hypoglycemia in critically ill patients, including continuous venovenous hemofiltration, inotropic support, or sepsis are absent or less common outside of the ICU (5).

It also remains unknown whether reported risks of hypoglycemia in ICU studies, which included primarily nondiabetic patients, also apply to patients with known diabetes. Several studies have demonstrated that the relationship of elevated blood glucose with clinical outcomes may be quantitatively and qualitatively different between patients with and without a diagnosis of diabetes. Hyperglycemic patients with diabetes have been found to have lower mortality than nondiabetic hyperglycemic patients; they may also derive less or no benefit from intensive glycemic control (3,6–10). It is possible that a similar divergence exists for hypoglycemia as well.

Because the majority of hospitalized patients with diabetes are treated in the general ward, it is important to understand the relationship of hypoglycemia in diabetic patients in the general ward with clinical outcomes. To this end, we examined whether hypoglycemia in patients with diabetes hospitalized in the general ward is associated with adverse outcomes. We assessed the relationship between the number and severity of hypoglycemic episodes with in-hospital mortality and the length of hospital stay. We also evaluated the association between hypoglycemia and outpatient mortality 1 year after discharge.

RESEARCH DESIGN AND METHODS

— We conducted a retrospective cohort study to investigate whether hypoglycemia in diabetic patients hospitalized in the general ward is associated with poor clinical outcomes. We evaluated the relationship between *1*) the number of days with hypoglycemia (predictor variable) during the hospital admission and *2*) hospital mortality (primary outcome variable). We also conducted three secondary analyses: *1*) the relationship between *a*) the lowest recorded blood glucose and *b*) hospital mortality; *2*) the relationship between *a*) the number of days with hypoglycemia and *b*) outpatient mortality within 1 year from discharge; and *3*) the relationship

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between *a*) the number of days with hypoglycemia and *b*) the change from the length of stay (LOS) expected based on the diagnosis-related group (DRG). The institutional review board at Partners HealthCare approved the study and waived the need for informed consent.

Study patients and settings

Patients with diabetes who were admitted to a 734-bed teaching hospital between January 2003 and August 2004 were studied. Patients with diabetes were identified through a combination of computational analysis of the text of their physician notes with billing and laboratory data using a previously validated algorithm. When compared with a manual record review, the algorithm has a sensitivity of 96.2% and a specificity of 98.0% (11). Pregnant women and newborns, patients who had stayed in an ICU during their hospitalization, patients who had received intravenous total parenteral nutrition, and patients for whom point-of-care blood glucose results were not available were excluded from the analysis.

Outcome and exposure measures

Hypoglycemia was defined as blood glucose ≤50 mg/dl. Only point-of-care blood glucose levels were used in the analysis. Changes from the expected length of hospital stay were computed as the difference between the actual LOS and the mean LOS for the patient's DRG (12). A modified Charlson Comorbidity Index was computed using administrative billing codes (13) excluding diabetes because all study subjects had this diagnosis. Patient-day weighted mean blood glucose during the hospital stay was calculated as the mean of all blood glucose readings on a single day averaged over the course of the hospital stay (14). Glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease formula (15). An elevation in liver function test results was quantified as the average of the fold difference of alanine aminotransferase and aspartate aminotransferase levels over the upper limit of normal. Normal values were imputed in place of missing laboratory data. Complications of diabetes (nephropathy, neuropathy, ophthalmopathy, and peripheral vascular disease) were ascertained from the ICD-9 billing codes reported for each patient up to the end of the study period. One inpatient or two outpatient billing codes were required to confirm each diagnosis.

Data sources

Patient demographics, dates of death, admission and discharge dates, laboratory data, billing codes, discharge summaries, and outpatient physician notes were obtained from the Research Patient Data Registry, a large data warehouse that serves as a central clinical data repository for participating hospitals and clinics within the Partners HealthCare System. Computerized Physician Order Entry data were obtained from the hospital inpatient electronic health record. Point-of-care blood glucose data were obtained from the QC Manager system (Abbott Laboratories, Abbott Park, IL).

Statistical analysis

Summary statistics were constructed by using frequencies and proportions for categorical data and by using means, SDs, and medians and ranges for continuous variables. Summary statistics for patient demographics (age, sex, ethnicity, and health insurance) were calculated for individual patients. The remainder of the summary statistics were calculated for individual hospital admissions. Analysis of the outpatient mortality within 1 year from discharge was limited to the last admission during the study period for each unique patient. The univariate associations between the number of days with hypoglycemic episodes and clinical outcomes (inpatient mortality, mortality within 1 year after discharge, and length of hospital stay) were assessed using a Wilcoxon test for continuous variables and Fisher's exact test for binary variables.

To account for clustering within individual patients and to adjust for other covariates, a hierarchical (multilevel) multiple logistic regression model for the probability of inpatient death was constructed using a generalized estimated equation approach. A similar model was used for the analysis of the outpatient death within 1 year from discharge date including only the last hospital admission during the study period for each patient.

To determine the relationship between the number of days with hypoglycemic events and the length of hospital stay, we constructed a hierarchical (multilevel) multivariable mixed linear regression model with random effects to account for clustering within individual patients. Random cluster effects were used to generate the correlation structure for intracluster observations and to account for individual patient effect levels. All multivariable models included patient age, sex, ethnicity, health insurance, patient-day weighted mean blood glucose during hospital stay, length of hospital stay expected based on the DRG, and modified Charlson Comorbidity Index as covariates. *P* values were obtained using a type III test for all multivariable analyses. Significance thresholds were adjusted for multiple hypothesis testing using the Simes-Hochberg method (16,17). All analyses were performed with SAS statistical software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Hypoglycemia in hospitalized diabetic patients

We identified 5,190 admissions of patients with diabetes (excluding pregnant women and newborns) that took place between January 2003 and August 2004 and had point-of-care blood glucose testing results. Of these patients, 785 had stayed in an ICU during their hospitalization, and 37 received total parenteral nutrition. These 822 admissions were excluded from the analysis.

The final analytical dataset included 4,368 admissions of 2,582 unique patients. Median age at the time of admission was 66 years and median modified Charlson Comorbidity Index was 5 (Table 1). Most patients had sliding scale insulin ordered, and 2,700 (61.8%) received scheduled antihyperglycemic medications (either insulin or oral). Hypoglycemic events (blood glucose ≤50 mg/dl) were documented in 338 (7.7%) admissions. The average blood glucose level (measured using point-of-care testing) during a hypoglycemic episode was 41 mg/dl. Severe hyperglycemia (>300 mg/dl) was observed for 1,272 (29.1%) admissions, and in 169 (3.9%) admissions there were both severe hyperglycemia and hypoglycemia documented. In multivariable analysis the odds of a hypoglycemic episode increased by >2.5-fold for patients receiving scheduled insulin ($P < 0.0001$). Complications of diabetes and other comorbidities, GFR, liver function test abnormalities, and patient age were not associated with a change in risk for a hypoglycemic episode.

Frequency of hypoglycemia and patient mortality

In univariate analysis, inpatient mortality was 2.96% for patients who had at least one hypoglycemic episode during the hospital stay vs. 0.82% for patients who

Table 1—*Patient characteristics*

Total study admissions	4,368
Unique subjects	2,582
Mean age (years)*	63.6 ± 15.1
Female sex	1,325 (51.3)
Ethnicity	
White	1,517 (58.8)
Black	544 (21.1)
Hispanic	273 (10.6)
Other/unknown	248 (9.6)
Insurance	
Medicare	1,428 (55.3)
Medicaid	332 (12.6)
Commercial	800 (31.0)
Self-pay	22 (0.9)
Admission service	
Medical	2,702 (61.9)
Surgical	1,660 (38.0)
Unknown	6 (0.1)
Glomerular filtration rate (ml/min)	64.6 ± 38.4
Mean modified Charlson Comorbidities Index†	4.9 ± 3.3
Received sliding-scale insulin	3,479 (79.6)
Received scheduled insulin	1,427 (32.7)
Received oral antihyperglycemic agents	1,530 (35.0)
Received insulin secretagogues	1,069 (24.5)
Actual LOS (days)	4.9 ± 5.5
Deviation from DRG-based LOS (days)	−0.8 ± 5.0
Mean blood glucose (mg/dl)‡	168.8 ± 48.0
Mean days with hypoglycemia	0.1 ± 0.41
Deceased during the admission	43 (1.0)
Deceased within a year from discharge§	388 (17.9)

Data are *n*, *n* (%), or means ± SD. Aggregate patient-level characteristics (e.g., demographics) were calculated at the individual patient level, and aggregate admission-level characteristics (e.g., LOS) were calculated at the individual admission level. *At the time of the first study admission. †Diabetes was excluded from the computation of the index. ‡Patient-day weighted mean glucose level. §Calculated for the last study period admission of the 2,582 unique study patients.

had none ($P = 0.0013$). In a multivariable analysis adjusted for the patients' demographics, expected LOS, Charlson Comorbidity Index, GFR, complications of diabetes, and average blood glucose, the odds of inpatient mortality rose by 85.3% for each additional day with a hypoglycemic episode ($P = 0.009$). The odds of inpatient mortality also increased by 24.8% for each additional point of the Charlson Comorbidity Index ($P < 0.0001$). Patient age, GFR, and insulin secretagogue use during the admission had no significant relationship with inpatient mortality.

Mortality 1 year after discharge was 27.8% for patients who had at least one hypoglycemic episode vs. 14.1% for patients who had no hypoglycemic episodes ($P < 0.0001$). Univariate analysis showed a progressive increase in 1-year mortality from 14.1% for patients with no hypoglycemic episodes to 33.3% for patients with more than two hypoglycemic episodes (Fig. 1). Multivariable analysis of this dataset showed a 65.8% increase in mortality 1 year after discharge for each day with a hypoglycemic episode during the admission ($P = 0.0003$) and a 41.8% decrease for patients given insulin secretagogues during their hospitalization ($P = 0.0007$).

Degree of hypoglycemia and patient mortality

In univariate analysis of a subset of 338 admissions for which any hypoglycemia was documented, the mean lowest recorded blood glucose was 31.8 mg/dl for patients who died in the hospital vs. 40 mg/dl for those who did not ($P = 0.028$). Inpatient mortality rate increased progressively from 1.9% for patients whose lowest blood glucose was >39 mg/dl to 8.2% for those with lowest glucose <30 mg/dl (Fig. 2). In multivariable analysis, the odds of inpatient mortality increased threefold for every 10 mg/dl decrease in the lowest blood glucose ($P = 0.0058$). There was no significant relationship between the degree of hypoglycemia and mortality at 1 year after discharge.

Hypoglycemia and length of hospitalization

In univariate analysis, patients who had at least one episode of hypoglycemia stayed in the hospital 2.8 days longer than patients who did not have any hypoglycemic episodes ($P < 0.0001$). The difference between actual LOS and LOS expected for the DRG increased gradually from –1.0 days for patients with no hypoglycemia to 8.8 days for patients with >2 days with a hypoglycemic episode (Fig. 3).

In a multivariable analysis adjusted for the patients' demographics, expected LOS, Charlson Comorbidity Index, diabetes complications, GFR, and average blood glucose, the actual length of stay

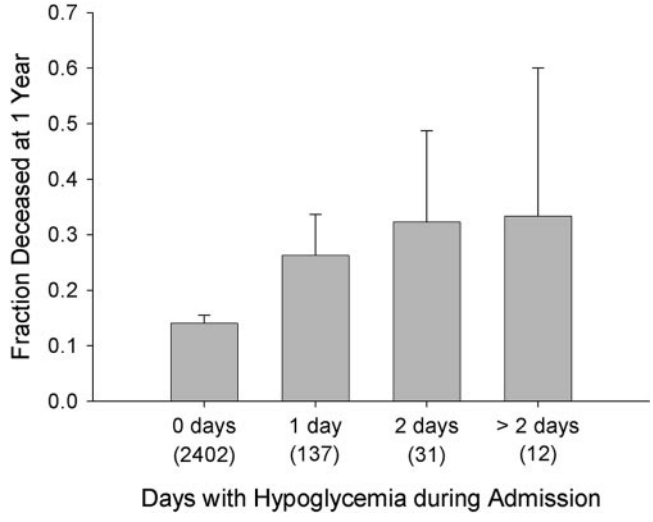

Figure 1—*Frequency of hypoglycemia and 1-year mortality. Bars indicate 95% CI. The number of admissions in each category is given in parentheses.*

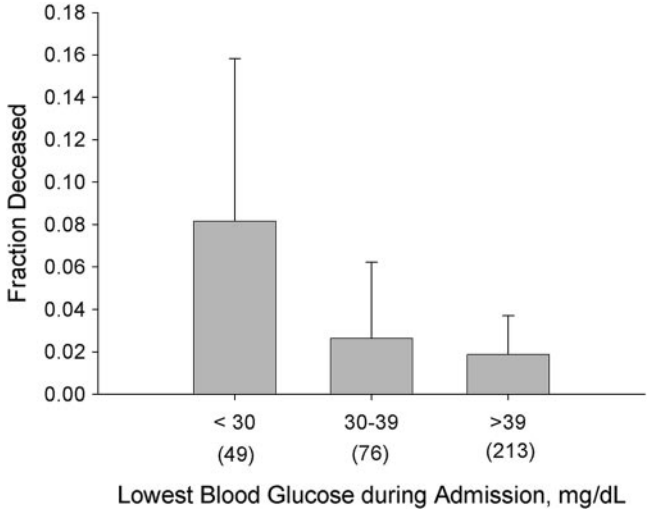

Figure 2—*Lowest blood glucose and inpatient mortality. The lowest blood glucose level recorded during the hospital stay was plotted against the fraction of patients who died during the admission for 338 patients who had at least one hypoglycemic episode documented in the hospital. Bars indicate 95% CI. The number of admissions in each category is given in parentheses.*

increased by 2.5 days compared with the average for the DRG for each additional day with a hypoglycemic episode ($P < 0.0001$). LOS also increased by 0.14 days for each additional point of the Charlson Comorbidity Index. There was no significant relationship between the lowest blood glucose level during the admission and the length of the hospital stay.

CONCLUSIONS — In this large retrospective cohort study of >4,000 admissions, we have focused on patients with known diabetes admitted to the general hospital ward. Mortality among hypoglycemic patients in this population was 3%, significantly lower than the 22–48% observed in the previously published investigations that included critically ill patients (18–21). Nevertheless, we have found a similarly strong relationship between hypoglycemia and in-hospital mortality as well as LOS. Unlike in some studies of the general hospital population (18,20), this relationship was dose dependent: both LOS and inpatient mortality increased gradually as the number of hypoglycemic episodes rose. A greater degree of hypoglycemia was also associated with an increase in inpatient mortality. Furthermore, an analysis of a data subset that contained only one admission per patient revealed a strong association between the number of episodes of hypoglycemia and outpatient mortality at 1 year after discharge from the hospital.

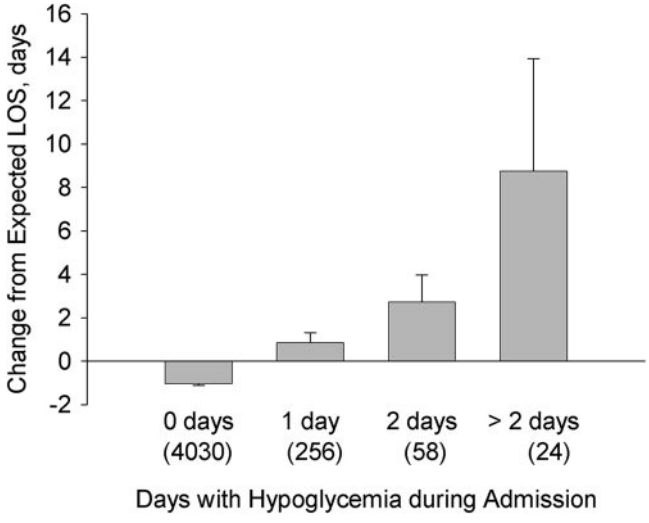

Figure 3—*Frequency of hypoglycemia and length of hospital stay. Bars indicate SEM. The number of admissions in each category is given in parentheses.*

Although the retrospective nature of our analysis does not allow a direct inference of causality, several explanations of this relationship can be hypothesized. On the one hand, hypoglycemia could affect outcomes directly by leading to falls, seizures, or death. It could also have an indirect effect by requiring adjustments of the patients' antihyperglycemic regimen or delays of tests and procedures, consequently leading to an extension of the hospital stay.

On the other hand, hypoglycemia could be a marker for disease severity. Studies in the general hospital population, including patients in the ICU, showed that decreased caloric intake, which could be related to disease-induced anorexia, was a significant contributor to hypoglycemia (5,18). Although our study design excluded critically ill patients, malnutrition is well described in less severely ill patients as well (22). The marker hypothesis is further supported by the strong association between hypoglycemia and outpatient mortality, a finding that is difficult to explain by a direct effect of inpatient hypoglycemia on survival.

Several recommendations can be made on the basis of our results. Sicker diabetic patients in the general ward should be monitored closely for the occurrence of hypoglycemia. Extra care should be taken to prevent hypoglycemic events in this population already at high risk for adverse events, with particular attention being paid to matching the antihyperglycemic regimen to the nutritional intake. At the same time, hypoglycemia among diabetic patients in the general ward could be interpreted as a warning sign of an impending clinical deterioration. It could therefore serve as a useful indicator for the necessity of increased monitoring, more aggressive treatment of infections, transitioning to a more intensive care setting, and case management.

Our study has a number of strengths. It is the first study to focus on patients with diabetes hospitalized in the general ward, by far the largest group of inpatients at high risk for hypoglycemia. It is one of the largest analyses of the phenomenon of inpatient hypoglycemia, encompassing >4,300 admissions of 2,582 individual patients. In addition, it included both inpatient and outpatient outcomes, thus helping to differentiate

possible immediate effects of hypoglycemia from a noncausal association.

This analysis has several limitations. The study included only patients admitted to a single academic hospital in Boston, Massachusetts, which could limit its generalizability to other geographic and health care settings. It was impossible to differentiate between type 1 and type 2 diabetes from the available data; therefore, it cannot be stated with certainty whether our findings apply to one or both conditions. However, statistically, most patients in the hospital have type 2 diabetes. Lack of nutrition information for individual patients has hindered the analysis of the causes of hypoglycemia. Furthermore, our data did not include descriptions of the types and severity of the immediate clinical sequelae (changes in mental status, loss of consciousness, or seizures) of the hypoglycemic episodes. We used point-of-care blood glucose levels in this study, the accuracy of which may have been limited, particularly at the lower glucose levels. On the other hand, central laboratory glucose levels used in many other studies are typically obtained much less frequently, possibly leading to an underestimation of the frequency and severity of hypoglycemia. In addition, unless blood samples for glucose measurement are routinely collected into tubes with a glycolysis inhibitor, the measured blood glucose level may be falsely lowered in patients with high white cell counts (23), precisely the patients at high risk for adverse outcomes. Finally, the retrospective nature of the study does not allow us to draw conclusions about causal relationships and may have led to a bias if missing data were distributed unevenly with respect to the outcomes analyzed.

In summary, hypoglycemia in diabetic patients hospitalized in the general ward was associated with increased inpatient and postdischarge mortality as well as with a prolonged LOS. Further studies are needed to establish a causal relationship. In the meantime, care should be taken to prevent hypoglycemia in this high-risk patient population.

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