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Relative Hypoglycemia in Diabetic Patients With Critical Illness

Timothy N. Kwan, MD[1,2]; Lara Zwakman-Hessels, MD[1,3,4]; Nada Marhoon, BSc[1,3]; Ray Robbins, PhD[1,3]; Johan Mårtensson, PhD[5]; Elif Ekinci, PhD[6,7]; Rinaldo Bellomo, MD[1,2,3,5]

Objectives: Relative hypoglycemia is a decrease in glucose greater than or equal to 30% below prehospital admission levels (estimated by hemoglobin A1C) but not to absolute hypoglycemia levels. It is a recognized pathophysiologic phenomenon in ambulant poorly controlled diabetic patients but remains unexamined during critical illness. We examined the frequency, characteristics, and outcome associations of relative hypoglycemia in diabetic patients with critical illness.

Design: Retrospective cohort study.

Setting: ICU of a tertiary hospital.

Patients: One-thousand five-hundred ninety-two critically ill diabetic patients between January 2013 and December 2017.

Interventions: None.

Measurements and Main Results: The median age of patients was 67 years (interquartile range, 60–75 yr). The median Acute Physiology and Chronic Health Evaluation III score was 53 (interquartile range, 40–68). Thirty-four percent of patients with diabetes experienced relative hypoglycemia (exposure) during their ICU admission. Such patients had higher glycemic lability, hemoglobin A1C levels, and Acute Physiology and Chronic Health Evaluation III scores. The hazard ratio for 28-day mortality of diabetic patients, censored at hospital discharge, for patients with relative hypoglycemia was 1.9 (95% CI, 1.3–2.8) and was essentially unchanged after adjustment for episodes of absolute hypoglycemia. After an episode of relative hypoglycemia, the hazard ratio for subsequent absolute hypoglycemia in the ICU was 3.5 (95% CI, 2.3–5.3).

Conclusions: In ICU patients with diabetes, relative hypoglycemia is common, increases with higher hemoglobin A1C levels, and is a modifiable risk factor for both mortality and subsequent absolute hypoglycemia. These findings provide the rationale for future interventional studies to explore new blood glucose management strategies and to substantiate the clinical relevance of relative hypoglycemia. (*Crit Care Med* 2020; 48:e233–e240)

Key Words: blood glucose; critical care; diabetes mellitus; hypoglycemia; intensive care; mortality

Glycemic management is an important component in the management of ICU patients. Multiple observational studies and assessment of data from randomized controlled trials have reported a strong and consistent association between absolute hypoglycemia (AH) (blood glucose $\leq$ 70 mg/dL or < 4 mmol/L) and mortality (1–4). Lower glucose levels correlate with stricter glucose control; however, there are conflicting data favoring either strict (80–110 mg/dL) or conventional (< 180 mg/dL) glucose control (5, 6). These inconsistent results may suggest that the occurrence of hypoglycemia and its associations with outcomes is affected by factors, possibly pre-ICU patient characteristics.

In particular, the risk of hypoglycemia and its associations may depend not only on the presence of diabetes but also on premorbid glycemic management (7). Current practice, however, does not take individual patient factors such as hemoglobin A1C into account when choosing a glycemic target (8). This approach exposes patients not only to AH but also to nonhypoglycemic fluctuations in blood glucose level of currently undetermined significance. One such fluctuation is relative hypoglycemia (RH).

RH is an established concept in outpatient diabetology. It has been defined as a symptomatic lowering of blood glucose level, which does not reach the threshold of AH (9). In people with poorly managed diabetes, RH can be induced by experimental insulin-glucose clamp studies. In such studies, a blood glucose reduction of approximately 30% is associated with the release of stress hormones, similar to that seen with AH. Furthermore, it produces autonomic and neuroglycopenic symptoms (10–16). The cutoff of 30% is logical and mirrors the standard definitions for AH, whereby a healthy individual with a normal mean blood glucose of 100 mg/dL (5.5 mmol/L; hemoglobin A1C 5.1%) would have RH at 70 mg/dL or below (a 30% reduction) (17). RH is an acute event; however, diagnosis requires some knowledge of previous glycemic control. Hemoglobin A1C provides a point of reference for chronic glycemic control because it is an estimate of average glucose levels over the previous 3 months (17). RH may be relevant to diabetic patients admitted to ICU, but this possibility has never been studied in the critical care setting, where special considerations apply.

In ICU patients with diabetes, symptoms associated with RH may not be detectable in the presence of sedation. Also, epinephrine, norepinephrine, cortisol, and glucagon levels are not routinely measured to detect a physiologic stress response to RH. Thus, the physiologic stress associated with RH is likely to go undiagnosed in the majority of such patients. Furthermore, as diabetes prevalence in the community is high, poor glycemic management relatively common, and tighter glucose blood levels are typically pursued in diabetic patients in a manner similarly to other ICU patients, RH may be frequent.

Accordingly, we aimed to examine the prevalence, characteristics, and associations of RH in critically ill diabetic patients. We hypothesized that RH would be common and that it would be independently associated with greater risk of AH and mortality.

MATERIALS AND METHODS

Study Design
We studied medical and surgical adult patients admitted to a tertiary ICU from January 2013 to December 2017 who had at least one glucose reading and an hemoglobin A1C measurement during their admission or within the previous 3 months. The presence of medical conditions including diabetes was according to diagnoses coded in the electronic medical records. When there were repeat admissions, only the most recent admission was included. Blood glucose levels were exclusively obtained from blood gas measurements to ensure the highest level of accuracy.

Patients were divided into subgroups according to their first hemoglobin A1C in the past 3 months: hemoglobin A1C less than 6.5%, 6.5–7.4%, and greater than or equal to 7.5%. This was because, for patients with hemoglobin A1C in the diabetic range (≥ 6.5%), the median hemoglobin A1C was 7.5%. The demographic and clinical features of patients within each of these three groups were obtained from the ICU database. Summary features of patients with and without RH were also derived using ICU glucose data. Average glucose was calculated with time-weighting, and change in glucose over time was quantified with the glycemic lability index (GLI) which is also a time-weighted statistic (18). AH was defined as a single episode of glucose less than or equal to 70 mg/dL, and RH was defined as a single episode of glucose greater than or equal to 30% below the average glucose level but not less than or equal to 70 mg/dL. The average glucose level was derived from hemoglobin A1C using a validated formula and hence was the average preadmission glucose over the previous 3 months (17).

The study was approved by the Human Research Ethics Committee of the Austin Hospital with a waiver for informed consent given the retrospective database anonymized nature of the study.

Glucose Control in the ICU
The study ICU provided relatively liberal glucose control with a glucose target between 180 and 250 mg/dL in diabetic patients (type 1 and 2) as previously reported (19). In patients without diabetes, the target glycemic level was between 100 and 180 mg/dL. Glucose control was achieved by continuous infusion of short-acting insulin (Actrapid). Blood glucose levels were monitored as clinically indicated by a blood gas analyzer, typically every 4 hours.

Statistical Analysis
The probability of developing RH and AH were compared over time with competing risk analysis (20). Mortality over 28 days after admission to ICU was also calculated according to RH with Kaplan-Meier survival curves.

The primary outcome of 28-day mortality and the secondary outcome of risk of AH were assessed using Cox regression, according to the presence of RH. Collinearity was quantified with the generalized variance inflation factor (GVIF) (21). Time was measured from the date of ICU admission. At baseline, time-dependent covariates were classified as being negative and were regarded as positive from when an event occurred. Time-dependent covariates were RH, AH, intubation, noninvasive ventilation, and continuous renal replacement therapy (CRRT). Categorical covariates were sex, admission source, emergency status of admission, whether the patient lived in their own home, and the presence of various comorbidities at admission: respiratory arrest, cardiac arrest, chronic respiratory disease, chronic renal failure, AIDS, hepatic failure, malignant lymphoma, metastases, leukemia/multiple myeloma, and immune compromise. Numerical covariates were hemoglobin A1C, time-weighted average glucose in ICU, GLI in ICU, age, number of glucose measurements, and Acute Physiology and Chronic Health Evaluation (APACHE) III (range 0–299). The multivariable models included terms with univariate significance p value of less than 0.2.

The 28-day mortality according to RH was recalculated with multivariate analysis in subpopulations according to AH, hemoglobin A1C, APACHE III, age, sex, and diabetes. These subpopulations were split by round figures close to the median. Our statistical analysis methodology was designed to mirror the recent Normoglycemia in Intensive Care Evaluation (NICE) trial hypoglycemia study (1).

Nonparametric statistical methods were used including the median, interquartile range (IQR), Mann-Whitney U test for continuous variables, and the chi-square test for binary variables. When more than two variables were compared, the Kruskal-Wallis test (one-way analysis of variance [ANOVA] on ranks) was used for a numerical outcome and ANOVA on a logistic regression model for a binary outcome. Kaplan-Meier curves and competing risk analysis curves were generated with standard statistical techniques (20). In cases where data on certain variables were missing, they were excluded from the respective analysis. Calculations were exclusively run on R 3.5.1 from the R Development Core Team (22). Statistical significance was set at p value of less than 0.05.

RESULTS

Study Participants

Out of 8,597 patients, a total of 1,592 patients were included in our final cohort (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

The median age of patients was 67 years (IQR, 60–75 yr). Fifty-three percent of admissions were surgical, 54% were emergencies, and 66% of patients were men. The median APACHE III score of patients was 53 (IQR, 40–68). The median hospital stay was 11 days (IQR, 6–21 d), and the mortality rate in hospital was 13%.

Compared to patients with hemoglobin A1C less than 6.5%, patients with hemoglobin A1C greater than or equal to 6.5% had a slightly lower APACHE III, stayed in hospital for a longer period, and were more likely to die in the hospital. However, these differences were not significant when stratified according to the three prespecified hemoglobin A1C ranges (**Table 1**).

Rates and Timing of Relative Hypoglycemia and Absolute Hypoglycemia

RH was common, with half of patients (48.3%) with hemoglobin A1C greater than or equal to 6.5% experiencing at least one episode during their ICU admission and two thirds of patients (64.7%) with hemoglobin A1C greater than or equal to 7.5% experiencing RH. The median time from ICU admission to RH

TABLE 1. Clinical Characteristics of Patients According to Hemoglobin A1C Levels

Variable	Hemoglobin A1C < 6.5%	Hemoglobin A1C 6.5–7.4%	Hemoglobin A1C ≥ 7.5%	p
N	634	462	496	–
Hemoglobin A1C (%)	5.8 (5.4–6.1)	6.9 (6.6–7.1)	8.5 (7.9–9.8)	< 0.001
Acute Physiology and Chronic Health Evaluation III	54 (42–69)	53 (42–68)	52 (38–67)	0.071
Age	68 (60–76)	70 (62–76)	65 (57–73)	< 0.001
Male	416 (65.6%)	306 (66.2%)	337 (67.9%)	0.703
Source of ICU admission				
Ward	138 (21.8%)	109 (23.6%)	71 (14.3%)	< 0.001
Operating room	344 (54.3%)	260 (56.3%)	276 (55.6%)	0.787
Emergency department	92 (14.5%)	56 (12.1%)	122 (24.6%)	< 0.001
Other hospital	60 (9.5%)	37 (8.0%)	27 (5.4%)	0.037
Surgical admission	338 (53%)	253 (55%)	268 (54%)	0.890
Living at home	503 (79.3%)	377 (81.6%)	407 (82.1%)	0.458
Emergency ICU admission	255 (54.6%)	187 (51.2%)	211 (55.5%)	0.463
Outcomes				
Died in hospital	98 (15.7%)	55 (12.0%)	55 (11.2%)	0.062
Died in ICU	54 (8.5%)	32 (6.9%)	37 (7.5%)	0.603
Hospital stay (d)	12 (7–22)	10 (6–19)	11 (6–21)	0.049
ICU stay (hr)	53 (26–109)	47 (25–90)	48 (23–112)	0.177
Intubated during admission	338 (53.3%)	247 (53.5%)	265 (53.4%)	0.999
Noninvasive ventilation during admission	26 (4.7%)	29 (7.4%)	24 (5.8%)	0.227
Continuous renal replacement therapy during admission	82 (12.9%)	38 (8.2%)	42 (8.5%)	0.013

Results are reported as median (interquartile range) or as n (%).
p is from the Kruskal-Wallis test for numerical outcomes or analysis of variance on a logistic regression model for binary outcomes.
p values not calculated for absolute sample size.

was 12 hours (IQR, 1.7–28 hr) (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

Factors Associated With Relative Hypoglycemia

There was a significant and positive association between the frequency of RH and hemoglobin A1C ($p < 0.001$; **Table 2**). Patients who experienced RH also had higher APACHE III scores ($p < 0.001$) and were more likely to be admitted to ICU as an emergency admission ($p < 0.001$; Table 2). They generally had poorer glycemic management as reflected by more episodes of AH ($p < 0.001$), a higher GLI ($p < 0.001$), and greater range of glucose levels ($p < 0.001$; Table 2). Finally, they had a higher unadjusted mortality rate ($p = 0.005$), stayed longer in hospital ($p = 0.026$), and received CRRT more frequently ($p < 0.001$; Table 2).

Multivariate logistic regression analysis demonstrated that greater hemoglobin A1C, lower mean glucose, and more frequent blood glucose measurements were independently associated with RH (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). There was mild collinearity (maximum GVIF[1/2 df] where df is the degrees of freedom: 1.72). This analysis was replicated: 1) including patients without diabetes (this analysis included patients from outside the sample size of this study, **Supplemental Fig. 3**, Supplemental

TABLE 2. Characteristics of Patients With Relative Hypoglycemia

Variable	Relative Hypoglycemia	No Relative Hypoglycemia	p
n	546	1,046	—
Acute Physiology and Chronic Health Evaluation III	58 (44–74)	51 (39–65)	< 0.001
Age	67 (59–75)	68 (60–75)	0.335
Male	67 (59–75)	68 (60–75)	0.335
Surgical admission	263 (48%)	596 (57%)	0.001
Living at home	450 (82.4%)	837 (80.0%)	0.277
Emergency ICU admission	269 (62.0%)	384 (49.4%)	< 0.001
Number of glucose measurements/day	6.8 (5.0–8.6)	7.0 (5.4–9.1)	0.026
Hemoglobin A1C (%)	7.8 (6.8–9.2)	6.4 (5.7–7.1)	< 0.001
Median baseline glucose (mg/dL)	177	137	< 0.001
Experienced AH episode	99 (18.1%)	41 (3.9%)	< 0.001
Experienced moderate AH	88 (16.1%)	39 (3.7%)	< 0.001
Experienced severe AH	11 (2.0%)	2 (0.2%)	< 0.001
Mean glucose (mg/dL)	173.8 (146.5–209.1)	178.7 (153.5–212.0)	0.048
Minimal glucose (mg/dL)	93.7 (77.5–113.5)	129.7 (108.1–153.1)	< 0.001
Maximal glucose (mg/dL)	268.4 (214.4–340.0)	237.8 (192.8–295.5)	< 0.001
SD of glucose (mg/dL)	48.3 (34.7–63.2)	32.0 (21.4–45.8)	< 0.001
Coefficient of variation of glucose	27.1 (21.5–33.9)	17.9 (12.9–23.9)	< 0.001
Glycemic lability index (mmol/L^2/hr.wk^{-1})	69.0 (38.6–138.9)	38.8 (15.0–82.1)	< 0.001
Intubated during admission	265 (48.5%)	585 (55.9%)	0.006
Noninvasive ventilation during admission	31 (7.2%)	48 (5.2%)	0.183
Continuous renal replacement therapy during admission	80 (14.7%)	82 (7.8%)	< 0.001
Hospital stay (d)	12 (7–23)	10 (6–19)	0.026
ICU stay (hr)	71 (38–141)	45 (23–87)	< 0.001
Died in hospital	90 (16.7%)	118 (11.4%)	0.005
Died in ICU	61 (11.2%)	62 (5.9%)	< 0.001

AH = absolute hypoglycemia.
Results are reported as median (interquartile range) or as n (%).
p is from the Mann-Whitney U test for numerical outcomes or χ^2 test for binary outcomes.
Baseline glucose estimated from hemoglobin A1C (17); AH defined as ≤ 70 mg/dL.
To convert glucose to mmol/L, divide values by 18.

Digital Content 1, http://links.lww.com/CCM/F242) and 2) including AH as a covariate (**Supplemental Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). Both diabetes and AH were significantly associated with RH, but the models essentially replicated the original findings.

Competing risk analysis revealed that at every time point, the frequency of RH was consistently and significantly more common if the hemoglobin A1C was greater than or equal to 6.5% (**Supplemental Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). By contrast, the frequency of AH was not associated with hemoglobin A1C (**Supplemental Fig. 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

Association Between Relative Hypoglycemia and Mortality

Mortality was higher in patients with RH of a greater magnitude (**Supplemental Fig. 7**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). This trend occurred irrespective of hemoglobin A1C but was more pronounced for those with a lower hemoglobin A1C. This unadjusted trend also resembles the increase in mortality that occurred with a greater absolute decline in glucose (**Supplemental Fig. 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). In both relative and absolute measures of decrease in glucose, there was evidence of a dose response (Supplemental Figs. 7 and 8, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

The Kaplan-Meier plot also demonstrated a significant unadjusted association between RH and mortality (**Fig. 1**). The median time to death after the first episode of RH was 10.8 days.

All covariates with univariate significance p value of less than 0.2 were entered into a Cox regression model (**Supplemental**

Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). In the adjusted model, the hazard ratio of 28-day mortality according to RH was 1.9 (95% CI, 1.3–2.8) (**Fig. 2**). To check the internal consistency of this measure, the model was optimized by stepwise removal of the least significant covariate if p value of greater than 0.2 (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). In this further optimized model, the hazard ratio for mortality associated with RH was essentially unchanged at 1.8 (95% CI, 1.2–2.5) (**Supplemental Fig. 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

Cox regression modeling with optimized covariates was replicated within further subgroups. Subgroups based on hemoglobin A1C, APACHE III, age, gender, and diabetes similarly did not lead to altered hazard ratios (**Supplemental Fig. 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). There was similarly a consistent association between RH and 28-day mortality irrespective of the occurrence of AH. This was consistent with the observation that including AH as a time-dependent covariate had little effect on the point estimate of the effect size of RH (**Supplemental Fig. 11**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

Association With Absolute Hypoglycemia

Among patients with hemoglobin A1C greater than or equal to 6.5% who experienced AH, two thirds (66.7%) had a preceding episode of RH. Furthermore, the vast majority of patients (90.7%) who experienced AH also experienced RH at some point during their ICU admission. The proportion of AH preceded by RH had a significant and positive association with hemoglobin A1C (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/F242).

Furthermore, patients were significantly more likely to experience subsequent AH if they had at least one episode of RH (hazard ratio, 3.5; 95% CI, 2.3–5.3) (**Fig. 3**). RH and GLI as univariate measures of glycemic variation also had a significant association with AH ($p \leq 0.001$; **Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F242). If the GLI was also excluded, so that RH was the only measure of glycemic variability, the hazard ratio of AH according to RH was 3.6 (95% CI, 2.4–5.4).
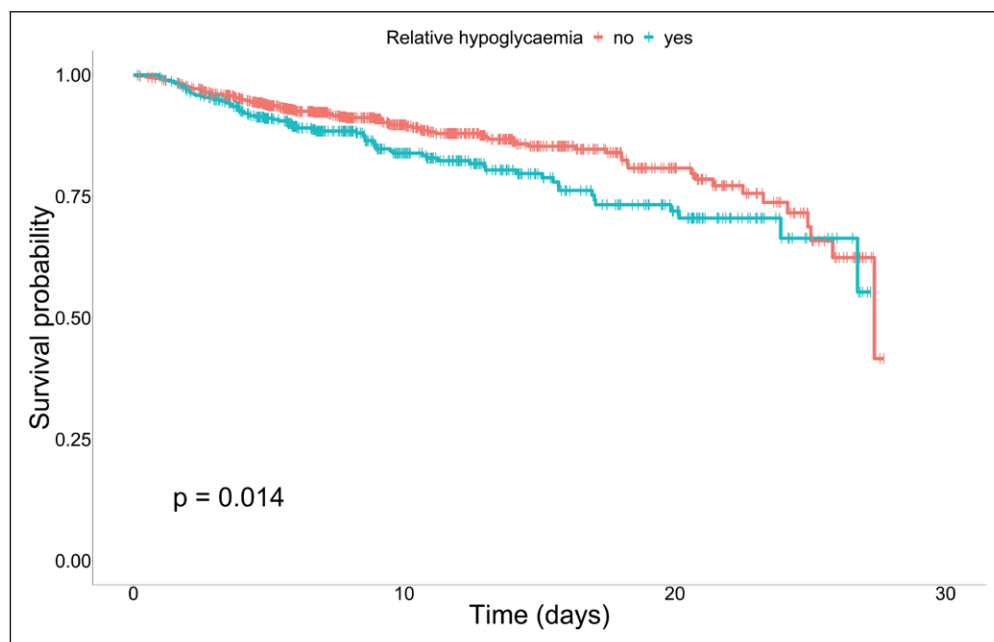
DISCUSSION

Key Findings

We systematically examined the concept of RH. We found that RH was common among

Figure 1. Rate of survival according to the presence of at least one episode of relative hypoglycemia. Kaplan-Meier estimates of survival.

Variable	Hazard ratio		p-value
Relative hypoglycemia		1.9 (1.3- 2.8)	0.002
Admitted from other hospital		0.8 (0.4- 1.5)	0.439
Admitted from operating room		0.8 (0.5- 1.4)	0.442
Admitted from emergency department		0.6 (0.4- 1.0)	0.075
HbA1c (%)		0.9 (0.8- 1.0)	0.074
Mean glucose (mmol/L)		1.0 (1.0- 1.1)	0.256
GLI (mmol/L^2/h·week^{-1})		1.0 (1.0- 1.0)	0.197
Age (10 years)		1.3 (1.1- 1.6)	0.003
Blood tests (10 measurements)		1.0 (0.9- 1.0)	0.226
APACHE III (10 points)		1.3 (1.2- 1.4)	<0.001
Emergency		2.2 (1.2- 4.1)	0.017
Lives at home		0.8 (0.5- 1.2)	0.250
Intubation		1.5 (1.0- 2.2)	0.036
CRRT		1.3 (0.9- 2.0)	0.210
Respiratory arrest		3.0 (1.0- 8.8)	0.045
Cardiac arrest		0.8 (0.4- 1.6)	0.578
Chronic cardiovascular disease		0.9 (0.5- 1.7)	0.733
Chronic renal failure		1.1 (0.7- 1.8)	0.621
AIDS		9.0 (1.0-78.4)	0.046
Hepatic failure		1.2 (0.7- 2.3)	0.504
Malignant lymphoma		0.3 (0.1- 1.8)	0.190
Metastases		1.0 (0.5- 2.1)	0.953
Immune compromise		1.5 (0.9- 2.4)	0.104

0.25 0.50 1.00 2.00 4.00 8.00

← Lower mortality   Higher mortality →

Figure 2. Hazard ratio of 28-d mortality with multivariate adjustment by Cox regression analysis. Relative hypoglycemia defined as a greater than or equal to 30% decrease from premorbid HbA1-derived estimates of glycemia. The following covariates were binary and recorded at the time of admission: respiratory arrest, cardiac arrest, chronic cardiovascular disease, chronic renal failure, AIDS, hepatic failure, cirrhosis, malignant lymphoma (also included leukemia), metastases, immune disease, and immunosuppressed. Hazard ratio greater than 1 indicates that binary variables were more likely to be positive. Maximum collinearity measured by generalized variance inflation factor$^{(1/2\ df)}$ was 1.47 (Acute Physiology and Chronic Health Evaluation [APACHE] III score). CRRT = continuous renal replacement therapy during admission as time-dependent covariate, *df* = degrees of freedom, GLI = glycemic lability index, HbA1c = hemoglobin A1C, Intubation = intubation during admission as time-dependent covariate.

critically ill diabetic patients, especially among those with poor chronic glycemic management. Furthermore, we found that RH was significantly and independently associated with all-cause mortality, a finding that persisted even after adjustment for the impact of AH and which was robust to multiple different modeling assumptions. Finally, RH was strongly associated with AH, and, importantly, preceded it in two thirds of cases.

Relationship With Existing Literature

Despite the physiologic parallels between AH and RH, RH has historically been considered harmless (9). Thus, no similar study of RH has ever been reported in the field of diabetology or critical care. Nevertheless, previous ICU studies have shown that there is an association between glucose variability and mortality (2, 4, 18, 23–27). Similarly, the NICE trial demonstrated that intensive glucose control could be detrimental, perhaps not only due to AH but also due to volatile glucose levels (6, 28). Four interventional pilot trials have demonstrated that more liberal therapies reduce glycemic variability and AH; however, to date, these studies have been underpowered to assess the possible impact on clinical outcomes (19, 28–30).

Some studies report an increased risk of hypoglycemia with higher hemoglobin A1C, whereas others report no difference (19, 31). In the ICU in the present study, glycemic targets were higher than in other studies. This likely affected the frequency of hypoglycemia.

Study Strengths and Limitations

Our study has several strengths. It is the first assessment of the epidemiology of RH in critically ill patients and, in fact, the first such study in the wider field of diabetology. Its findings are consistent with observations that demonstrate an association between glucose variability (which may in great proportion be affected by RH) and mortality, and t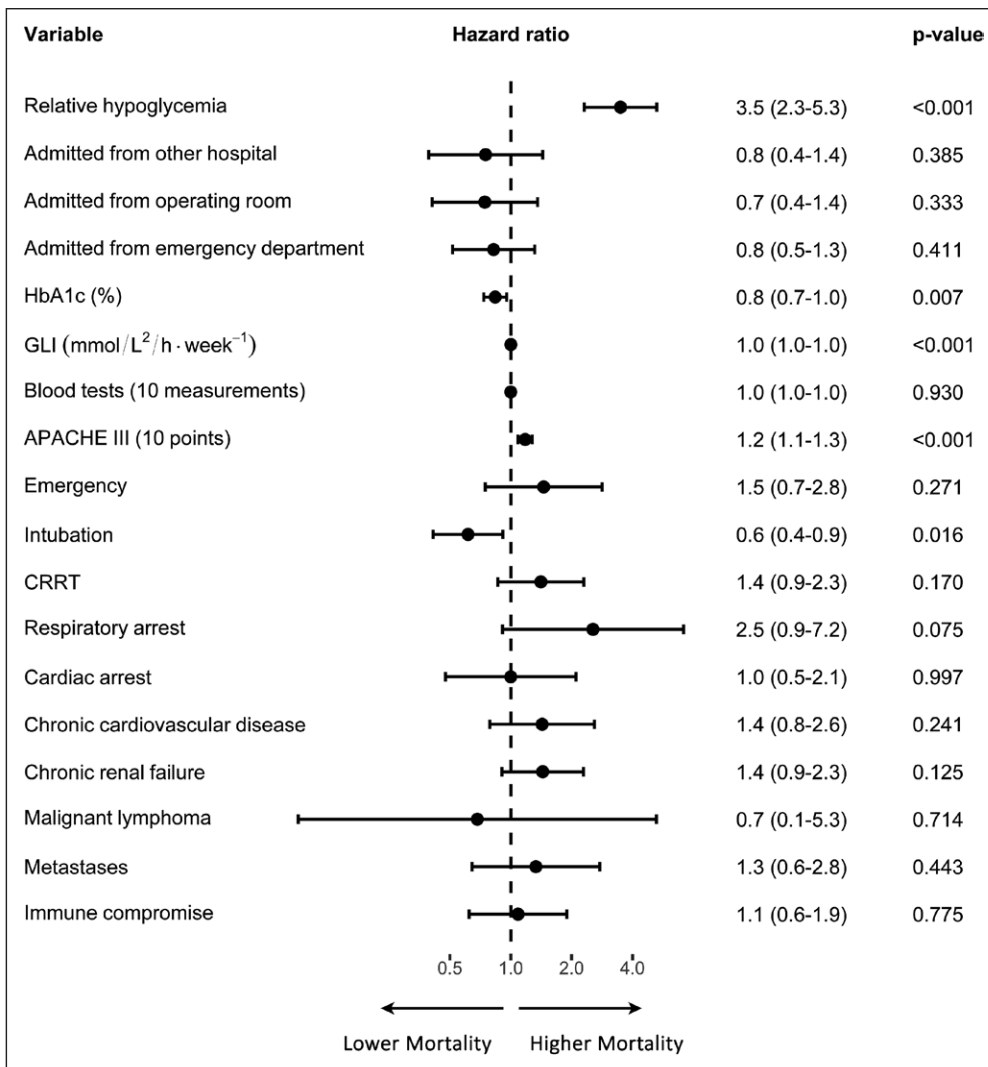hese findings are biologically plausible. We adjusted for confounders, and our results were found to be robust in both a larger and optimized set of covariates and after adjustment for the confounding effect of AH.

There are limitations in our data, as outpatient glycemic control could not be measured and could only be estimated from hemoglobin A1C. However, hemoglobin A1C is a well-validated

Figure 3. Hazard ratio of hypoglycemia occurring within 28 d with multivariate adjustment by Cox regression analysis. Relative hypoglycemia defined as a greater than or equal to 30% decrease from premorbid HbA1-derived estimates of glycemia. The following covariates were binary and recorded at the time of admission: respiratory arrest, cardiac arrest, chronic cardiovascular disease, chronic renal failure, malignant lymphoma (also included leukemia), metastases, and immune disease. Hazard ratio greater than 1 indicates that binary variables were more likely to be positive. Maximum collinearity measured by generalized variance inflation factor$^{(1/2\ df)}$ was 1.53 (Emergency). CRRT = continuous renal replacement therapy during admission as time-dependent covariate, df = degrees of freedom, GLI = glycemic lability index, HbA1c = hemoglobin A1C, Intubation = intubation during admission as time-dependent covariate.

is inevitable in this type of analysis and applied to the association between AH and mortality in the NICE trial (1). However, we sought to address this issue by competing risk analysis and our findings were robust to such analysis. Detection bias may have contributed to the observed associations of RH; however, this effect was probably small as the number of blood gases taken per day was within 3% for patients with RH, compared with no RH. Also, adjustment was made for the number of blood gases, and time-weighted measures were used. Finally, the study was based at a single ICU which limits its external validity (19, 31). However, the study ICU has all the typical characteristics of a tertiary ICU in a developed country and glucose control was delivered by an estimated greater than 300 ICU nurses and greater than 50 ICU fellows, registrars, residents, and attending specialists.

Implications of Study Findings

Our findings have implications for the optimization of glycemic management in critically ill diabetic patients (28). In particular, they suggest caution in allowing or even forcing glucose levels to drop substantially below a diabetic patient's baseline level. They reveal a novel relationship between acute and chronic glycemic control. Furthermore, they imply that knowledge of premorbid hemoglobin A1C may be important in setting glycemic targets. Indeed, the repeatedly reported lack of association between hyperglycemia and mortality in critically ill diabetic patients may be explained by the fact that such hyperglycemic levels may be normal for these patients. Finally, independent of concerns about RH per se, the known risks of AH, the strong association between RH and AH, and the fact that AH was preceded by RH in two thirds of cases all imply that an episode of RH should, at least, trigger closer monitoring and, if possible, upward adjustment of glycemic targets.

This study suggests the need for prospective multicenter studies to confirm the clinical significance of RH. Further studies will also be required to better understand the relationship

approximation of overall glycemic control in the preceding 3 months and has a strong correlation with the gold standard measurement of average glucose (correlation = 0.84; $p < 0.0001$) (17).

As an observational study, there are several limitations. Although many confounders were adjusted for, many yet undiscovered or unmonitored confounders were not. Adjustment for GLI and mean glucose as covariates may have minimized the real effects of RH due to collinearity. Furthermore, as this was an observational study, the extent to which RH contributed to morbidity and mortality could not be fully distinguished from the extent to which it was a consequence of existing morbidity. Immortal time bias also complicates the interpretation of our results, as the measurement of RH is mutually exclusive with the patient being 1) dead or 2) having left ICU. Such bias may inflate the effect size estimate. This bias

between RH and clinical outcomes, including the effect of insulin regimen and other diabetic management strategies.

This novel perspective of the relationship between acute and chronic glycemic control offers a reinterpretation of randomized control trial results that differ in terms of optimal glycemic target (6, 32–38). It is possible that intensive glucose control may have been unsafe in patients with high baseline blood glucose levels by producing physiologic stress associated with RH. Accordingly, this study provides rationale for future interventional trials with individualized glycemic targets based on chronic glycemic control.

CONCLUSIONS

RH is a measure of glycemic management known to have pathophysiologic similarities with AH. During ICU admission, RH occurs frequently in diabetic patients with poor pre-ICU glycemic management and is a modifiable independent risk factor for mortality in such patients. In addition, the likelihood of AH, another independent predictor of mortality in ICU patients, is markedly increased following an episode of RH. In their aggregate, these findings suggest the need for additional investigations into the epidemiology, significance, and possible prevention of RH.

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