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ORIGINAL ARTICLE

Glucose Control, Diabetes Status, and Mortality in Critically Ill Patients: The Continuum From Intensive Care Unit Admission to Hospital Discharge

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Abstract

Objective: To describe the relationships among glycemic control, diabetes mellitus (DM) status, and mortality in critically ill patients from intensive care unit (ICU) admission to hospital discharge.

Patients and Methods: This is a retrospective investigation of 6387 ICU patients with 5 or more blood glucose (BG) tests and 4462 ICU survivors admitted to 2 academic medical centers from July 1, 2010, through December 31, 2014. We studied the relationships among mean BG level, hypoglycemia (BG level <70 mg/dL [to convert to mmol/L, multiply by 0.0555]), high glucose variability (coefficient of variation ≥20%), DM status, and mortality.

Results: The ICU mortality for patients without DM with ICU mean BG levels of 80 to less than 110, 110 to less than 140, 140 to less than 180, and at least 180 mg/dL was 4.50%, 7.30%, 12.16%, and 32.82%, respectively. Floor mortality for patients without DM with these BG ranges was 2.74%, 2.64%, 7.88%, and 5.66%, respectively. The ICU and floor mean BG levels of 80 to less than 110 and 110 to less than 140 mg/dL were independently associated with reduced ICU and floor mortality compared with mean BG levels of 140 to less than 180 mg/dL in patients without DM (odds ratio [OR] [95% CI]: 0.43 (0.28-0.66), 0.62 (0.45-0.85), 0.41 (0.23-0.75), and 0.40 (0.25-0.63), respectively) but not in patients with DM. Both ICU and floor hypoglycemia and increased glucose variability were strongly associated with ICU and floor mortality in patients without DM, and less so in those with DM. The independent association of dysglycemia occurring in either setting with mortality was cumulative in patients without DM.

Conclusion: These findings support the importance of glucose control across the entire trajectory of hospitalization in critically ill patients and suggest that the BG target of 140 to less than 180 mg/dL is not appropriate for patients without DM. The optimal BG target for patients with DM remains uncertain.

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A large body of literature has found that dysglycemia—hyperglycemia, hypoglycemia, and increased glucose variability—is independently associated with mortality in critically ill patients.[1-7] This association is stronger for patients without diabetes (DM) than it is for patients with DM.[8-14]

Few studies have reported on the relationships of these domains of glycemic control to mortality, or other important clinical outcomes, in non–critically ill hospitalized patients.[15] Hyperglycemia is strongly associated with mortality and morbidity, especially postoperative infection, in patients with DM undergoing cardiovascular surgery.[16,17] Other investigations have reported an association of hyperglycemia with adverse outcomes in patients admitted to general medical wards with community-acquired pneumonia[18] and exacerbations of chronic obstructive pulmonary disease.[19] Hypoglycemia has been associated with increased hospital length of stay, complications, and mortality in non–critically ill patients with DM.[20-22] Finally, glucose variability has been associated with deleterious outcomes in various populations in non–intensive care unit (ICU) settings.[23-25]

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The transition from the ICU to general floor care has major implications for glucose management of the hospitalized patient. The higher nurse to patient ratio in the ICU facilitates greater frequency of blood glucose (BG) measurement and the implementation of protocols using intravenous insulin infusions to treat hyperglycemia. This stands in contrast to the lesser resources available on the wards for glycemic control. Limited data exist evaluating the changes in glucose metrics that occur in patients after discharge from the ICU to the general wards.[26] Although major emphasis has been placed on glycemic control in the ICU, glycemic control has not been as rigorously studied or pursued in hospitalized patients cared for outside of the ICU. No studies to date have reported on glucose control metrics spanning the entire trajectory of hospitalization, from ICU admission to hospital discharge of ICU survivors. We hypothesized that dysglycemia—hyperglycemia, hypoglycemia, and increased glucose variability—occurring in both settings, the ICU as well as the floors after ICU discharge, is independently associated with mortality. To test this hypothesis, we performed a 2-center cohort investigation of critically ill patients and their continuum of glycemic control from the ICU through to hospital discharge.

MATERIALS AND METHODS

Patients and Settings

This is a retrospective analysis of patients admitted to ICUs at Tufts Medical Center in Boston, Massachusetts, a tertiary medical center, and Stamford Hospital in Stamford, Connecticut, a university-affiliated teaching hospital, from July 1, 2010, through December 31, 2014. Patients at Tufts Medical Center were admitted to the medical and surgical ICUs, each a 10-bed unit. Patients at Stamford Hospital were admitted to the 16-bed mixed medical-surgical ICU. A total of 10,619 patients were admitted to the ICUs during this period. The study exclusion criteria included readmission to the ICU during the same hospitalization, an admitting diagnosis of diabetic ketoacidosis or hyperosmolar hyperglycemic state, and fewer than 5 BG tests during ICU care (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). The 2 remaining cohorts consisted of 6387 ICU patients and the 4462 ICU survivors with at least 1 BG test after ICU discharge. Diabetes status was determined prospectively at the time of ICU admission based on all available clinical information obtained from patients, surrogates, and the electronic medical record.

The 2 ICUs at Tufts Medical Center were organized using a closed model, with intensivist-led multidisciplinary teams providing patient care. The Stamford ICU had a hybrid organization, with mandatory consultation required from a critical care physician and care provided by an intensivist-led multidisciplinary team. The nurse to patient ratio was 1:2 or 1:1 in both ICUs depending on patient acuity. In contrast, the nurse to patient ratio on the general medical and surgical wards ranged from 1:4 to 1:8. Hospitalists or non—hospital-based private physicians provided medical care to the patients, often with the assistance of medical and surgical house staff or mid-level practitioners (physician assistants or nurse practitioners).

Glucose Control and Metrics

At Tufts Medical Center, the BG target was 100 to 150 mg/dL (to convert to mmol/L, multiply by 0.0555) in the medical ICU and 95 to 135 mg/dL in the surgical ICU. The BG target in the Stamford Hospital ICU was 90 to 120 mg/dL. These targets were identical for patients with and without DM. Nurses used point-of-care devices to monitor BG levels; most measurements were made using glucose meters, testing primarily arterial or central venous blood when in the ICU; capillary point-of-care testing was the main source of measurement for patients on the ward. Paper-based protocols guided insulin therapy, and the frequency of monitoring ranged from hourly to every 4 to 6 hours based on the nurses' assessment of clinical need. In contrast, glucose control on the general floors was not standardized. Instead, the attending physician was responsible for writing glycemic control orders, including insulin orders and point-of-care testing. In both institutions, physicians had access to electronic order sets, specifically including basal-bolus—prandial insulin administration; neither institution used a

dedicated team led by an endocrinologist to assist in the management of dysglycemia. We defined dysglycemia as abnormalities in the following domains of glycemic control: hyperglycemia, mean BG levels of 140 mg/dL or greater (without DM) and 180 mg/dL or greater (with DM); hypoglycemia, BG level less than 70 mg/dL; and increased glucose variability, coefficient of variation (standard deviation of the mean BG level/mean BG level [CV]) of 20% or greater. The extensive literature regarding glucose metrics and mortality in critically ill patients provided the rationale for these choices.[1-14] In particular, several observational investigations have reported a different relationship between mean glycemia during ICU stay and mortality for patients with and without DM[8-13]; moreover, a recently published before-and-after interventional study in critically ill patients using 2 BG targets found a reduction in severity-adjusted mortality rates in patients with DM treated with a higher BG target than that used in patients without DM.[14]

Data Aggregation

Data elements at Tufts Medical Center, including demographic characteristics, comorbidities, diagnostic category, severity of illness scores, mechanical ventilation, ICU length of stay (LOS), hospital discharge status, and ICU BG values, were extracted from an ICU database (ICUTracker; Medical Decision Network LLC), providing automated data aggregation and reporting, and at Stamford Hospital from the comprehensive ICU database maintained by 1 of us (J.S.K.) and linked to the hospital's data information system to retrieve laboratory values. General medical and surgical ward BG values and hospital LOS were extracted from the hospitals' central data information systems.

Statistical Analyses

This investigation includes 2 cohorts of patients: 6387 patients admitted to the ICU with at least 5 BG values during ICU care and the 4462 ICU survivors with at least 1 BG value during floor care. The primary outcomes were ICU and floor mortality. We report continuous values as mean ± SD or median (interquartile range;) and made comparisons using the *t* test or the Wilcoxon

TABLE 1. Clinical Characteristics and Glucose Metrics of the Entire Cohort of 6387 ICU Patients, Stratified by Diabetes Status[a,b]

Variable	All patients			Patients without diabetes			Patients with diabetes		
	Survivors (n=5826)	ICU nonsurvivors (n=561)	*P* value	Survivors (n=4145)	ICU nonsurvivors (n=369)	*P* value	Survivors (n=1681)	ICU nonsurvivors (n=192)	*P* value
Clinical characteristics									
Age (y), median (IQR)	65 (52-77)	70 (58-81)	<.001	63 (49-77)	68 (55-81)	<.001	68 (59-77)	72 (60-80)	.02
APACHE IV PM (%), mean ± SD	16.5 ± 18.5	27.8 ± 56.3	<.001	15.5 ± 18.1	55.6 ± 27.5	<.001	18.9 ± 19.1	58.8 ± 27.6	<.001
Ventilation (%)	45.71	89.13	<.001[c]	46.95	88.08	<.001[d]	42.65	91.15	<.001[e]
ICU LOS (d), median (IQR)	2.8 (1.5-5.8)	4.0 (1.8-8.6)	<.001	2.9 (1.5-6.0)	4.2 (1.9-9.4)	<.001	2.5 (1.4-5.0)	3.8 (1.8-8.2)	<.001
Glucose metrics									
Mean BG (mg/dL), median (IQR)	127 (113-145)	136 (140-161)	<.001	121 (110-135)	132 (117-151)	<.001	148 (129-176)	145 (127-174)	.51
Coefficient of variation (%), median (IQR)	19.5 (14.2-27.2)	25.7 (18.4-35.2)	<.001	17.4 (13.1-23.2)	23.4 (27.3-32.2)	<.001	26.8 (19.7-36.3)	30.0 (21.1-40.6)	.001
Hypoglycemia, BG <70 mg/dL (%)	16.58	35.05	<.001[f]	14.23	33.06	<.001[g]	22.37	39.06	<.001[h]

[a]APACHE = Acute Physiology and Chronic Health Evaluation; BG = blood glucose; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; PM = predicted mortality.
[b]SI conversion factor: To convert BG values to mmol/L, multiply by 0.0555.
[c]Difference between proportions: 95% CI, 40.27 to 46.19.
[d]Difference between proportions: 95% CI, 37.08 to 44.61.
[e]Difference between proportions: 95% CI, 43.00 to 52.82.
[f]Difference between proportions: 95% CI, 14.40 to 22.69.
[g]Difference between proportions: 95% CI, 13.92 to 24.00.
[h]Difference between proportions: 95% CI, 9.45 to 24.24.

TABLE 2. Clinical Characteristics and Glucose Metrics of the 4462 Floor Patients, Stratified by Diabetes Status[a,b]

Variable	All patients			Patients without diabetes			Patients with diabetes		
	Survivors (n=4275)	Nonsurvivors (n=187)	*P* value	Survivors (n=2769)	Nonsurvivors (n=119)	*P* value	Survivors (n=1506)	Nonsurvivors (n=68)	*P* value
Clinical characteristics									
Age (y), median (IQR)	65 (53-77)	77 (66-85)	<.001	63 (49-77)	79 (66-88)	<.001	2.3 (1.4-4.8)	4.3 (2.4-10.3)	<.001
APACHE IV PM (%), mean ± SD	16.5 (17.6)	42.9 (24.4)	<.001	15.9 (17.5)	42.9 (24.5)	<.001	17.6 (17.8)	42.8 (24.3)	<.001
Ventilation (%)[c]	46.83	68.98	<.001[d]	50.16	68.07	<.001[e]	40.70	70.59	<.001[f]
ICU LOS (d), median (IQR)	2.7 (1.5-5.8)	4.8 (2.3-10.0)	<.001	2.9 (1.7-6.4)	4.9 (2.3-9.5)	<.001	2.3 (1.4-4.8)	4.3 (2.4-10.3)	<.001
Glucose metrics									
Mean BG (mg/dL), median (IQR)	135 (118-163)	145 (122-166)	.02	125 (112-142)	141 (121-162)	<.001	166 (142-194)	150 (134-198)	.08
Coefficient of variation (%), median (IQR)	22.7 (14.8-32.2)	25.7 (17.4-36.8)	.001	19.1 (12.1-26.9)	21.6 (15.6-31.5)	.001	30.3 (23.0-38.9)	32.0 (23.5-40.0)	.58
Hypoglycemia, BG <70 mg/dL (%)	22.73	36.36	<.001[g]	17.91	30.25	.001[h]	31.61	47.06	.01[i]

[a]APACHE = Acute Physiology and Chronic Health Evaluation; BG = blood glucose; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; PM = predicted mortality.
[b]SI conversion factor: To convert BG values to mmol/L, multiply by 0.0555.
[c]Ventilation occurring during ICU care.
[d]Difference between proportions: 95% CI, 14.83 to 28.87.
[e]Difference between proportions: 95% CI, 8.55 to 26.37.
[f]Difference between proportions: 95% CI, 17.34 to 40.62.
[g]Difference between proportions: 95% CI, 6.62 to 21.07.
[h]Difference between proportions: 95% CI, 4.08 to 21.50.
[i]Difference between proportions: 95% CI, 2.99 to 28.16.

rank sum test, as appropriate. We report categorical values as percentages and made comparisons using the χ^2 test. We compared patients with and without DM, as well as survivors and nonsurvivors, for the ICU and floor cohorts.

We analyzed the relationship of glucose metrics to mortality: mean BG level of 80 to less than 110, 110 to less than 140, 140 to less than 180, and at least 180 mg/dL; CV less than 20%, 20% to less than 30%, and 30% or greater; and hypoglycemia less than 70 mg/dL and less than 40 mg/dL, stratifying these results by DM status. We chose these categories to remain concordant with the literature reporting on the relationship of glucose metrics to mortality in the critically ill.[1-14] We performed a multivariable analysis to assess the independent effect of glucose metrics on mortality using the Acute Physiology and Chronic Health Evaluation IV predicted mortality.[27] This comprehensive model uses, in part, a broad array of physiologic parameters from the first 24 hours of ICU admission, as well as age, chronic health conditions, mechanical ventilation, and more than 90 different ICU admission diagnoses, to derive a discrete prediction of hospital mortality. We performed an analysis of the relationship between mean BG level and mortality during ICU and floor care using the small subset of patients from the Stamford Hospital cohort with available hemoglobin A_{1c} (HbA_{1c}) values (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). We assessed the interaction of ICU and floor dysglycemia metrics on mortality in ICU survivors by calculating mortality for each of the metrics under 4 different conditions: not present either in the ICU or on the floor, not present in the ICU but present on the floor, present in the ICU but not on the floor, and present in the ICU and on the floor. Finally, we assessed the cumulative association of dysglycemia metrics with mortality. A $P<.05$ was defined as the threshold of statistical significance. We used the MedCalc statistical package, version 15.4 (MedCalc Software) for statistical analysis.

RESULTS

Table 1 and Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org)

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describe key clinical characteristics and glucose metrics of the 6387 patients stratified by DM status and survivor status. For patients with and without DM, age, ICU LOS, percentage undergoing mechanical ventilation, and Acute Physiology and Chronic Health Evaluation IV predicted mortality were higher in nonsurvivors than in ICU survivors. The percentages of patients with hypoglycemia and glucose variability were higher in nonsurvivors for patients with and without DM, whereas the mean BG level was higher in nonsurvivors in the no DM group but similar for DM survivors and nonsurvivors.

Table 2 and Supplemental Table 4 detail key clinical characteristics and glucose metrics of the 4462 patients who survived to ICU discharge and had at least 1 BG value during floor care, stratified by DM status and survivor status. The profile of glucose metrics for patients with and without DM was the same for this floor cohort as for the ICU cohort.

Figure 1 illustrates the relationship between mean BG level and mortality during ICU and floor care, respectively, stratified by DM status. Among patients without DM in both settings, an increasing mean BG level was associated with increased mortality (*P* for trend <.001 for both). In patients with DM in both settings there was no clear relationship between mean BG level and mortality. Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org) provides a more detailed description of the relationships between each of the 3 glucose metrics and mortality in the ICU and on the floor, stratified by DM status.

Table 3 displays the results of univariable and multivariable analyses of the relationship of glucose metrics with mortality for patients with and without DM. In the ICU and on the floor, in patients without DM, mean BG levels of 80 to less than 110 mg/dL and 110 to less than 140 mg/dL were strongly associated with reduced risk of mortality compared with the range of 140 to less than 180 mg/dL and in the ICU mean BG level of at least 180 mg/dL was strongly associated with increased risk of mortality compared with the range of 140 to less than 180 mg/dL. In contrast, in patients with DM there was no clear relationship between any range of mean BG levels and mortality in either setting.

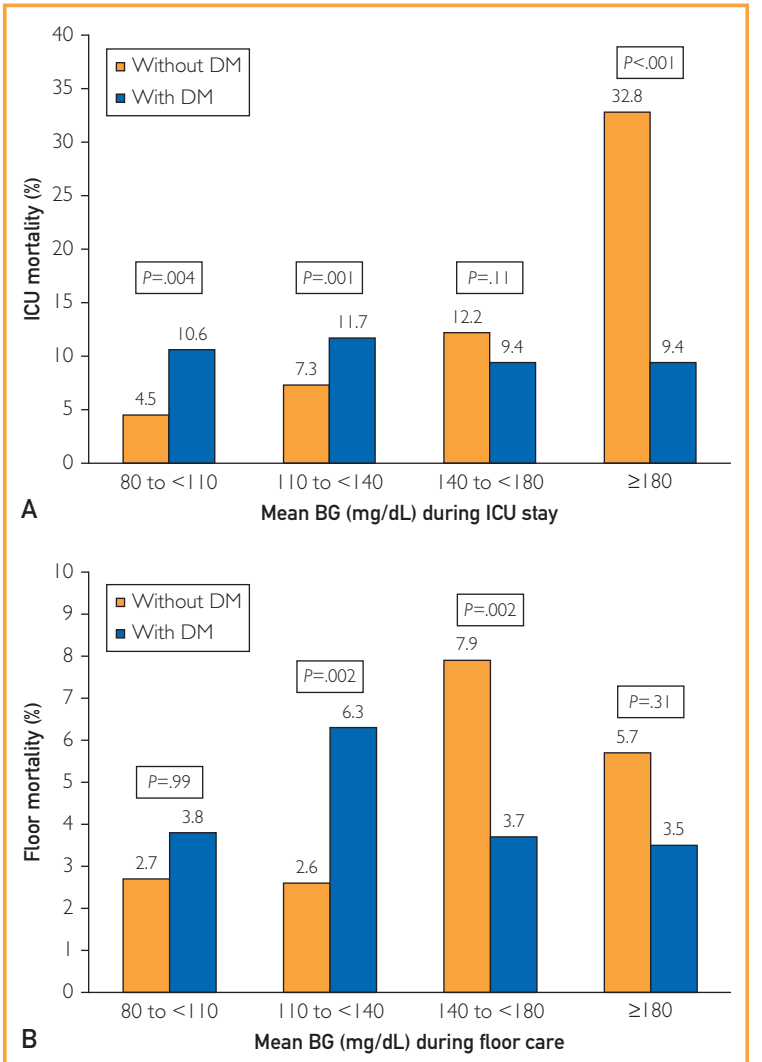

FIGURE 1. A, Relationship between mean blood glucose level during intensive care unit stay and ICU mortality, stratified by diabetes mellitus status. To convert BG values to mmol/L, multiply by 0.0555. B, Relationship between mean blood glucose level during floor stay and floor mortality, stratified by diabetes mellitus status. To convert BG values to mmol/L, multiply by 0.0555. BG = blood glucose; DM = diabetes mellitus; ICU = intensive care unit.

Hypoglycemia was associated with mortality for patients with and without DM in both settings. Finally, in patients without DM, increased glucose variability was strongly associated with mortality in the ICU and less so during floor care. In patients with DM in the ICU, increased glucose variability was associated with mortality on univariable but not multivariable analysis, but there was no clear

TABLE 3. Univariable and Multivariable Analyses of the Association of Glucose Metrics With Mortality, Stratified by Diabetes Status[a,b]

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ICU				
No diabetes				
Mean BG (mg/dL)				
80 to <110	0.34 (0.24-0.49)	<.001	0.43 (0.28-0.66)	<.001
110 to <140	0.56 (0.44-0.74)	<.001	0.62 (0.45-0.85)	.003
140 to <180	Reference		Reference	
≥180	3.53 (2.31-5.41)	<.001	2.12 (1.22-3.67)	.008
Coefficient of variation				
<20%	Reference		Reference	
20% to <30%	2.15 (1.67-2.78)	<.001	1.48 (1.09-2.00)	.01
≥30%	4.71 (3.60-6.16)	<.001	2.37 (1.70-3.30)	<.001
Hypoglycemia (mg/dL)				
BG <70	2.98 (2.36-3.76)	<.001	1.59 (1.20-2.12)	.001
BG <40	7.65 (4.94-11.84)	<.001	3.60 (2.02-6.40)	<.001
Diabetes				
Mean BG (mg/dL)				
80 to <110	1.14 (0.63-2.07)	0.66	1.27 (0.62-2.60)	.52
110 to <140	1.23 (0.81-1.82)	0.17	1.23 (0.81-1.87)	.32
140 to <180	Reference		Reference	
≥180	1.00 (0.66-1.51)	0.99	0.79 (0.47-1.33)	.38
Coefficient of variation				
<20%	Reference		Reference	
20% to <30%	1.16 (0.75-1.78)	0.50	1.09 (0.66-1.80)	.73
≥30%	1.67 (1.12-2.49)	0.01	0.98 (0.60-1.61)	.95
Hypoglycemia (mg/dL)				
BG <70	2.22 (1.62-3.04)	<.001	1.16 (0.79-1.69)	.45
BG <40	2.67 (1.52-4.68)	<.001	2.25 (1.15-4.38)	.02
Floor				
No diabetes				
Mean BG (mg/dL)				
80 to <110	0.32 (0.18-0.57)	<.001	0.41 (0.23-0.75)	.004
110 to <140	0.32 (0.21-0.49)	<.001	0.40 (0.25-0.63)	<.001
140 to <180			Reference	
≥180	0.70 (0.34-1.46)	0.34	0.55 (0.25-1.18)	.13
Coefficient of variation				
<20%			Reference	
20% to <30%	1.35 (0.87-2.10)	0.18	1.18 (0.74-1.89)	.48
≥30%	1.91 (1.22-3.01)	.005	1.49 (0.91-2.42)	.11
Hypoglycemia (mg/dL)				
BG, <70	1.99 (1.33-2.97)	<.001	1.54 (0.99-2.39)	.05
BG, <40	2.75 (1.65-4.59)	<.001	2.63 (1.51-4.58)	<.001
Diabetes				
Mean BG (mg/dL)				
80 to <110	1.03 (0.23-4.49)	.97	0.93 (0.18-4.84)	.94
110 to <140	1.77 (0.96-3.27)	.07	1.87 (0.97-3.58)	.06
140 to <180	Reference		Reference	
≥180	0.95 (0.52-1.76)	.88	1.06 (0.56-2.01)	.86
Coefficient of variation				
<20%	Reference		Reference	
20% to <30%	0.59 (0.29-1.22)	.15	0.49 (0.22-1.06)	.07
≥30%	0.86 (0.46-1.58)	.62	0.51 (0.26-1.00)	.05
Hypoglycemia (mg/dL)				
BG <70	1.92 (1.18-3.13)	.009	1.13 (0.66-1.94)	.66
BG <40	1.88 (0.97-3.67)	.06	1.62 (0.79-3.32)	.18

[a]BG = blood glucose; ICU = intensive care unit; OR = odds ratio.

[b]SI conversion factor: To convert BG values to mmol/L, multiply by 0.0555.

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relationship between glucose variability and mortality in patients with DM during floor care.

Figure 2 and Table 4 illustrate the cumulative association of dysglycemic metrics with mortality for patients in both settings, stratified by DM status. In patients without DM, the independent association effect of dysglycemia was found to be cumulative. Multivariable analysis found that compared with patients without DM without dysglycemia (mean BG level <140 mg/dL, no hypoglycemia, and CV <20%), patients without DM with all 3 manifestations of dysglycemia had a nearly 4-fold increase in the odds of mortality in the ICU, and for the ICU survivors, a nearly 3-fold increase in the odds of mortality during floor care. In contrast, these associations were not observed in patients with DM.

Finally, Figure 3 describes the interaction of dysglycemia occurring during ICU or floor care for patients without and with DM. In patients without DM, the occurrence of any of the 3 dysglycemic metrics during floor care was associated with numerically higher mortality regardless of the presence or absence of the same metric in the ICU. In patients with DM, this relationship was seen for hypoglycemia only.

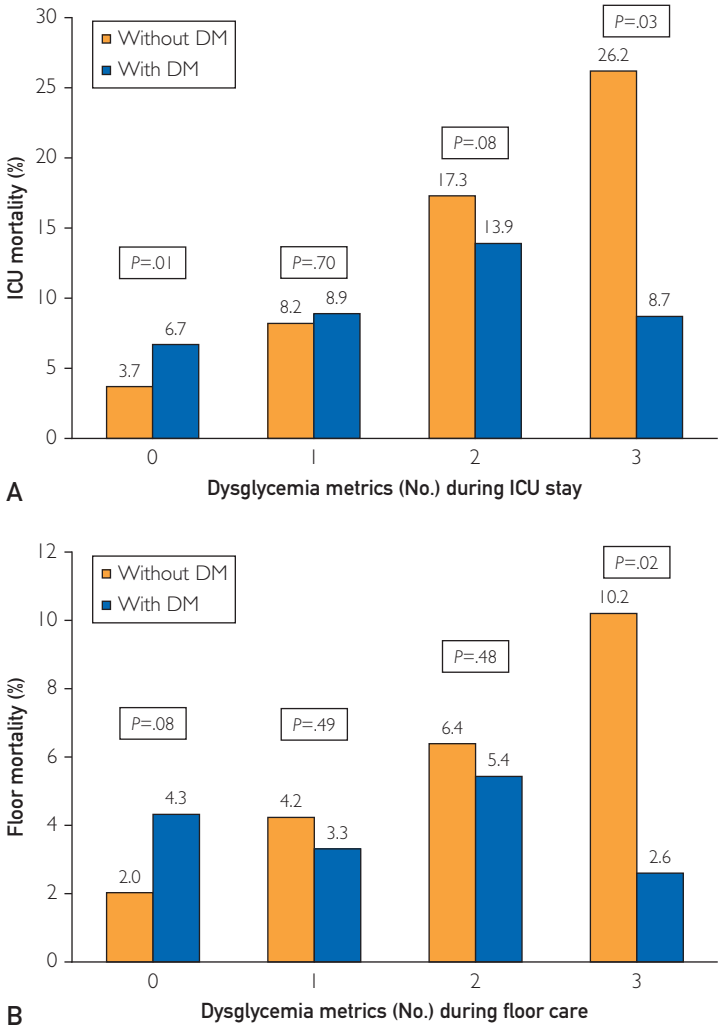

FIGURE 2. A, Relationship between dysglycemia metrics in the intensive care unit and mortality, stratified by diabetes mellitus status. B, Relationship between dysglycemia metrics during floor care and mortality, stratified by diabetes mellitus status. BG = blood glucose; DM = diabetes mellitus; ICU = intensive care unit.

DISCUSSION

This 2-center cohort study investigated the association between dysglycemia—hyperglycemia, hypoglycemia, and glucose variability—and mortality stratified by DM status in a large cohort of critically ill patients across the continuum of care from ICU admission to discharge from the hospital. Salient findings included the following: (1) in patients without DM, a mean BG level of 80 to less than 140 mg/dL was strongly associated with a reduced risk of ICU mortality compared with a mean BG level of 140 to less than 180 mg/dL during ICU care and during floor care, but there was no clear relationship between mean BG level and mortality for patients with DM in either setting; (2) high glucose variability (CV, ≥20%) in patients without DM was independently associated with increased risk of mortality in both settings, but in patients with DM this relationship was seen during ICU care only; and (3) hypoglycemia (BG level <70 mg/dL) was associated with mortality in all patients in both settings. Finally, in patients without DM, the association of dysglycemia with mortality was cumulative; compared with patients without dysglycemia, patients with all 3 manifestations of dysglycemia had nearly 4- and 3-fold odds of mortality in the ICU and on the floor, respectively. To our knowledge, this is the first report on the association of glucose control with mortality in a cohort of critically ill patients that spans the entire continuum of hospitalization.

TABLE 4. Univariable and Multivariable Analyses of the Cumulative Association of Dysglycemia With Mortality, Stratified by Diabetes Status[a,b]

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ICU[c]				
No diabetes				
No dysglycemia			Reference	
1 dysglycemia metric	2.31 (1.72-3.11)	<.001	1.69 (1.20-2.37)	.003
2 dysglycemia metrics	5.41 (4.08-7.18)	<.001	2.53 (1.81-3.54)	<.001
3 dysglycemia metrics	9.19 (5.62-15.03)	<.001	3.90 (2.13-7.14)	<.001
Diabetes				
No dysglycemia			Reference	
1 dysglycemia metric	1.37 (0.84-2.21)	.20	0.95 (0.54-1.68)	.87
2 dysglycemia metrics	2.26 (1.42-3.62)	<.001	1.01 (0.58-1.77)	.96
3 dysglycemia metrics	1.33 (0.44-4.03)	.61	0.48 (0.12-1.96)	.36
Floor[d]				
No diabetes				
No dysglycemia			Reference	
1 dysglycemia metric	2.13 (1.26-3.61)	.005	1.44 (0.81-2.56)	.21
2 dysglycemia metrics	3.29 (2.00-5.39)	<.001	2.28 (1.36-3.83)	.002
3 dysglycemia metrics	5.47 (2.54-11.81)	<.001	2.90 (1.26-6.69)	.01
Diabetes				
No dysglycemia			Reference	
1 dysglycemia metric	0.76 (0.33-1.73)	.51	0.55 (0.22-1.39)	.20
2 dysglycemia metrics	1.27 (0.60-2.67)	.53	0.85 (0.38-1.87)	.68
3 dysglycemia metrics	0.59 (0.18-1.95)	.37	0.26 (0.07-1.02)	.05

[a]ICU = intensive care unit; OR = odds ratio.

[b]Dysglycemia metrics: mean blood glucose level, 140 mg/dL or greater (to convert to mmol/L, multiply by 0.0555) (no diabetes) or 180 mg/dL or greater (diabetes); hypoglycemia, less than 70 mg/dL; and coefficient of variation, 20% or greater.

[c]The ICU multivariable model includes Acute Physiology and Chronic Health Evaluation IV predicted mortality.

[d]The floor multivariable model includes Acute Physiology and Chronic Health Evaluation IV predicted mortality and intensive care unit length of stay.

Relationship of Investigation to Previous Literature

A large body of observational literature has found that these 3 domains of glycemic control—hyperglycemia, hypoglycemia, and glucose variability—are independently associated with mortality in critically ill patients.[1-13] Data from randomized trials of intensive insulin therapy confirmed the independent association of hypoglycemia[28,29] and glucose variability[28] with mortality. In addition, differences in the relationship between glucose metrics and mortality when comparing patients with and without DM, noted in the present investigation, align with an emerging literature in various ICU populations.[2,8-13] Notably, these investigations reported glucose control metrics associated with ICU care only. We chose the "reference" level of mean BG of 140 to 180 mg/dL because this BG range has been chosen by prominent guideline writing groups as an appropriate target for all ICU patients,[30,31] based on the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) multicenter randomized controlled trial of intensive insulin therapy, demonstrating higher 90-day mortality in patients treated with a BG target of 80 to 110 mg/dL compared with the conventional arm, treated with a BG target of 140 to 180 mg/dL.[32]

In contrast, little is known about the effects of glycemic derangements during floor care after ICU care. A limited literature has corroborated the adverse effect of hyperglycemia,[15-17] hypoglycemia,[18-20] and increased glucose variability[21-23] on mortality, morbidity (especially infectious complications), or both in patients treated outside of the ICU. However, none of these investigations spanned the entire trajectory of a patient's hospital stay, including both ICU and floor glucose metrics.

The intensity of glucose control in the 2 centers included in this investigation contrasts sharply with data from a recently published observational investigation that reported the per-patient mean ± SD BG level in 55,245 patients from 576 US hospitals admitted to an ICU and transferred to a general ward.[26] Bersoux et al[26] compared the last 72 hours of ICU care with the first 72 hours of general ward care. The mean BG level decreased from approximately 179 mg/dL to 175 mg/dL during the 72 hours before ICU transfer and from approximately 174 mg/dL to 168 mg/dL in the first 72 hours of general ward care, with a corresponding gradual decrease in the standard deviation over this period. These data, not stratified by DM status, demonstrate a "loose" degree of glycemic control, with the mean BG level just below the upper limit of 180 mg/dL of the target range proposed by major guideline writing groups.[30,31] In contrast, individual patient mean BG levels in those with DM during ICU and floor care in the current investigation were 147 mg/dL (range, 129-175 mg/dL) and 165 mg/dL (range, 141-194 mg/dL), respectively, and considerably lower in patients without DM. Moreover, these data, from a large, representative sample of US hospitals, do not describe the relationship of glucose metrics to mortality.

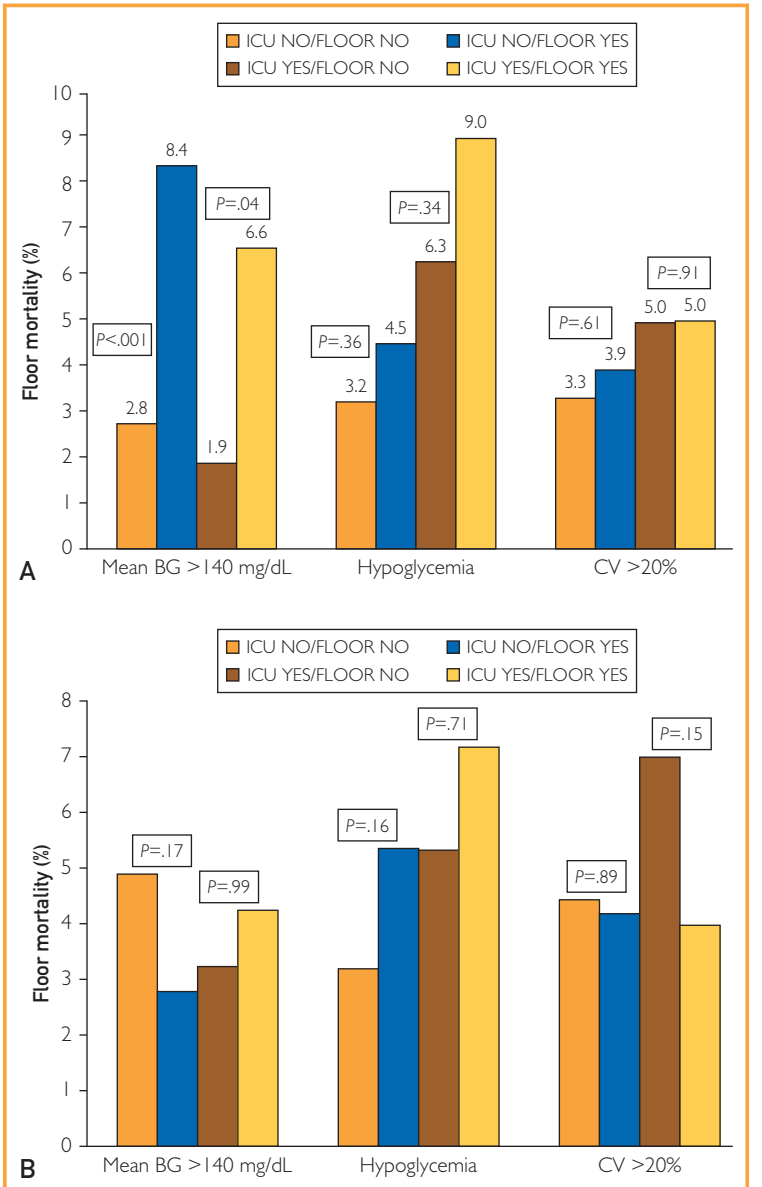

FIGURE 3. A, Interactions between intensive care unit (ICU) and floor glucose metrics and their relationship to floor mortality in patients without (A) and with (B) diabetes. BG = blood glucose; CV = coefficient of variation; ICU = intensive care unit.

Strengths and Limitations of the Study

The strengths of this investigation include the size of the cohort and its heterogeneous nature, including patients admitted with a variety of medical and surgical diagnoses, increasing its external validity. In addition, the data set includes a rich array of clinical and glucose control parameters, allowing detailed analyses. One limitation is the absence of measures of disease severity after initial admission to the ICU, impacting the strength of the multivariable model evaluating the independent association of glucose metrics during floor care to mortality. Second, the analysis does not include any information regarding insulin dosing, corticosteroid administration, or nutritional support. Third, although we determined DM status prospectively at the onset of ICU admission based on all available information, these decisions may not have been completely accurate because a substantial percentage of patients may have had previously undiagnosed diabetes. Along these lines, the data set includes HbA_{1c} measurements from only a small minority of patients from 1 center. Inaccurate attribution of DM status may have impacted these findings. Recent literature has suggested that of patients with DM, the intensity of glycemic control before ICU admission, reflected by HbA_{1c} levels,

likely modulates the relationship between glycemia during ICU care and mortality.[33-35] Finally, the major limitation of the study is its retrospective design. Importantly, note that although the association between dysglycemia and increased risk of hospital complications and death is clear, it is likely that dysglycemic states are also markers of disease severity occurring in acutely ill patients as the result of stress or due the presence of organ dysfunction.[15] Therefore, the conclusions from this observational cohort study can be considered hypothesis generating only, rather than proof of causality.

Clinical Implications of the Findings

Previously published interventional and observational investigations of the relationship between dysglycemia and outcomes in critically ill patients have focused primarily on glucose control during ICU care. This raises the possibility that differences in the degree of effective glucose control—avoidance of hyperglycemia, hypoglycemia, and minimizing glucose variability—outside of the ICU may have confounded the results of these studies.

These data strengthen the case for a BG target between 80 and 140 mg/dL in patients without DM, a range of glycemia associated with the lowest mortality during ICU as well as floor care. The appropriate target range for critically ill patients with DM remains unclear. As noted previously, we cannot stratify outcomes of patients with DM based on HbA_{1c} levels. Previous literature has suggested that the relationship between mean glycemia and mortality in patients with DM and low HbA_{1c} levels (eg <7%) is similar to that of patients without DM—increasing glycemia is associated with higher rates of mortality. However, in patients with DM with high HbA_{1c} levels, higher mean glycemia during critical illness is associated with lower mortality.[33-35] The hypothesis that BG targets should be based on preadmission glycemia has recently been evaluated in a 2-year before-and-after investigation that used 2 different BG targets of 80 to 140 mg/dL in patients without DM and patients with DM with HbA_{1c} levels less than 7% vs 110 to 160 mg/dL for patients with DM with HbA_{1c} levels of 7% or greater.[14] This study reported lower adjusted mortality for patients with DM in the interventional cohort.

CONCLUSION

In this large, heterogeneous cohort of ICU survivors, dysglycemia occurring during ICU as well as floor care was strongly associated with mortality in patients without DM, and less so in patients with DM. Although these conclusions cannot be considered as proof of causality, the data in this investigation provide a rationale for testing the hypothesis that the creation of successful programs for glucose control outside of the ICU may result in higher survival of critically ill patients admitted to the ICU.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **APACHE** = Acute Physiology and Chronic Health Evaluation; **BG** = blood glucose; **DM** = diabetes mellitus; **CV** = coefficient of variation; **HbA_{1c}** = hemoglobin A_{1c}; **ICU** = intensive care unit; **LOS** = length of stay; **OR** = odds ratio; **PM** = predicted mortality

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