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Hypoglycemia but Not Hyperglycemia Is Associated with Mortality in Critically Ill Patients with Diabetes

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Significance of the Study

- In patients with diabetes, hypo- but not hyperglycemia was associated with increased mortality, whereas in patients without diabetes, both hyper- and hypoglycemia were associated with adverse outcome. Blood glucose levels might need differential approaches depending on concomitant diseases.

Keywords
Glucose · Intensive care unit · Critically ill patients · Stress hyperglycemia · Hypoglycemia · Glucose deviation

Abstract
Background: Both severe hyperglycemia (>200 mg/dL) and hypoglycemia (≤70 mg/dL) are known to be associated with increased mortality in critically ill patients. Therefore, we investigated associations of a single episode of blood glucose deviation (concentration either ≤70 mg/dL and/or >200 mg/dL) during an intensive care unit (ICU) stay with mortality in these patients. ***Methods:*** A total of 4,986 patients (age 65 ± 15 years; 39% female; 14% type 2 diabetes [T2DM] based on medical records) admitted to a German ICU in a tertiary care hospital were investigated retrospectively. The intra-ICU and long-term mortality of patients between 4 and 7 years after their ICU submission were assessed. ***Results:*** A total 62,659 glucose measurements were analyzed. A single glucose deviation was associated with adverse outcomes compared to patients without a glucose deviation, represented by both intra-ICU mortality (22 vs. 10%; OR 2.62; 95% CI 2.23–3.09; $p < 0.001$) and long-term mortality (HR 2.01; 95% CI 1.81–2.24; $p < 0.001$). In patients suffering from T2DM hypoglycemia (30 vs. 13%; OR 2.94; 95% CI 2.28–3.80; $p < 0.001$) but not hyperglycemia (16 vs. 14%; OR 1.05; 95% CI 0.68–1.62; $p = 0.84$) was

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associated with mortality. ***Conclusion:*** In patients with diabetes, hypo- but not hyperglycemia was associated with increased mortality, whereas in patients without diabetes, both hyper- and hypoglycemia were associated with adverse outcome. Blood glucose concentration might need differential approaches depending on concomitant diseases.

Introduction

Both severe hyperglycemia (>200 mg/dL) and hypoglycemia (≤70 mg/dL) are known to occur frequently and constitute established risk factors for mortality in critically ill patients [1–4].

Hyperglycemia during critical illness is usually termed "stress hyperglycemia" and at least in part considered as adaptive and physiological, especially in sepsis [5]. In septic patients, hyperglycemia up to a certain degree is even considered to be beneficial, as increased levels of blood glucose concentration might be a way to ensure sufficient supply of glucose to peripheral cells in case of hypoperfusion [6, 7]. On the other hand, hyperglycemia, especially severe hyperglycemia defined as blood glucose concentration >200 mg/dL, was reported to be associated with adverse outcome and considered as a bad prognostic marker in various diseases, e.g., sepsis, acute myocardial infarction (AMI), and pulmonary embolism [8, 9]. Further, patients suffering from both AMI and even moderate hyperglycemia (160–200 mg/dL) were reported to experience adverse outcomes [10–12].

Tight glucose control, i.e., targeting blood glucose concentration <110 mg/dL, failed to improve, and even worsened, outcomes in patients admitted to an intensive care unit (ICU), probably partly due to iatrogenic hypoglycemia [13–15].

Hypoglycemia was reported to be associated with adverse outcomes and increased mortality rates in critically ill patients [1, 16]. Diabetes as a primary disease, intensive insulin therapy, renal and hepatic failure, adrenal insufficiency, and failure to follow the algorithms for glucose management represent frequent causes for hypoglycemia in ICU patients [17, 18]. Common consequences and reactions to hypoglycemia are functional brain failure, with irreversible brain injury in case of profound, ongoing hypoglycemia, cardiac rate and rhythm disturbances, and insufficient glucose supply of organs in general [17, 19]. Hypoglycemia remains one of the most relevant factors worsening patients' prognosis [20], especially in conditions with increased demand of glucose as in septic patients.

Type 2 diabetes (T2DM) is a common concomitant disease in patients admitted to an ICU [21]. Patients suffering from T2DM are prone to hyperglycemic derailment [21–24], but due to both oral antidiabetics and exogenous insulin therapy, these patients are more likely to suffer from hypoglycemia as well [21]. Interestingly, in patients suffering from diabetes and AMI, the associations of hyperglycemia and mortality were reported to be less clear, probably due to cellular adaptations to high blood glucose concentrations [11, 12].

Therefore, we investigated the associations of as little as a single episode of blood glucose deviation (concentration either ≤70 mg/dL or >200 mg/dL) during an ICU stay with mortality (1) in critically ill patients and (2) in patients suffering or not suffering from diabetes.

Methods

Patients admitted to the ICU of a tertiary care hospital were investigated retrospectively. Patients were included between January 2004 and December 2009. Follow-up of patients was performed retrospectively between May 2013 and November 2013. We included all patients with data on both (1) minimum and maximum glucose concentration during an ICU stay and (2) mortality. Admission diagnoses were, e.g., sepsis (n = 522), AMI (n = 1,316), pulmonary embolism (n = 127), acute heart failure (n = 532), and cardiopulmonary resuscitation (n = 372). Data on mortality were collected upon review of medical records (COPRA patient data management system; COPRA System GmbH, Berlin, Germany) or telephone interviews. The endpoint of the study was death from any cause. We report two timepoints: short-term (intra-ICU) mortality (available for 4,986 patients) and long-term mortality (available for 4,645 patients). The data of a part of this cohort have been analyzed in another context previously [25]. The diagnosis of T2DM was made based upon medical history.

Laboratory Analysis

Blood samples were drawn with standard care from both arterial and venous lines. Laboratory parameters were obtained from the Department of Clinical Chemistry at the Jena University Hospital. All blood glucose concentrations obtained during the patients' ICU stay were included in this analysis. In total, we included 62,659 glucose measurements.

Calculation of the Simplified Acute Physiology Score II and the Acute Physiology and Chronic Health Evaluation II Score

The initial Simplified Acute Physiology Score II (SAPS2) and Acute Physiology and Chronic Health Evaluation II (APACHE2) score were calculated by the treating physician within 24 h of admission as reported before [26, 27].

Statistical Analysis

Statistical analysis was performed using SPSS (22.0, SPSS Inc., USA) and MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium; www.medcalc.org; 2018) and

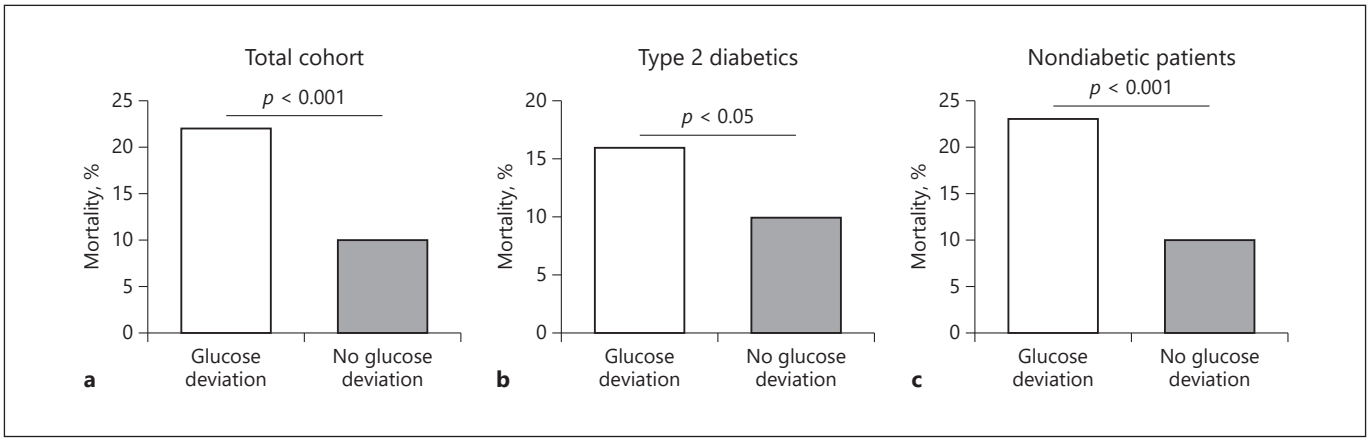

Fig. 1. A single glucose deviation was associated with increased intra-ICU mortality in the overall cohort (22 vs. 10%; OR 2.62; 95% CI 2.23–3.09; $p < 0.001$) (**a**), patients suffering from T2DM (16 vs. 10%; OR 1.73; 95% CI 1.10–2.73; $p = 0.02$) (**b**), and patients without T2DM (30 vs. 13%; OR 2.94; 95% CI 2.28–3.80; $p < 0.001$) (**c**). ICU, intensive care unit; T2DM, type 2 diabetes.

GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com). Normally distributed data are given as mean ± standard deviation and compared by Student's *t* test. The χ^2 test was applied to calculate differences between groups. Logistic regression was used to compare short-term mortality, Cox regression analysis was used to compare long-term mortality, and Kaplan-Meier curves were used to depict survival data. For the multivariate regression model, a backward variable elimination was performed. The elimination criterion was a *p* value >0.10. A *p* value <0.05 was considered statistically significant.

Results

A total of 4,986 nonconsecutive patients (age 65 ± 15 years; 39% female; 14% suffering from T2DM) were included. Of these, 1,507 patients were intubated. The mean duration of ICU stay was 105 h. Of the patients, 7.7% had a hypoglycemic episode during the ICU stay and 29.6% had a severe hyperglycemic episode; 34.6% suffered from either hypoglycemia (≤70 mg/dL) or hyperglycemia (>200 mg/dL) during the ICU stay, i.e., a glucose deviation. A single glucose deviation was associated with adverse outcomes compared to patients without a glucose deviation, higher intra-ICU mortality (22 vs. 10%; OR 2.62; 95% CI 2.23–3.09; $p < 0.001$) (Fig. 1) as well was higher long-term mortality (HR 2.01; 95% CI 1.81–2.24; $p < 0.001$) (Fig. 2).

On admission, patients who suffered from glucose deviation during their ICU stay were sicker as expressed by higher APACHE2 score ($p < 0.001$) and SAPS2 ($p < 0.001$), had higher lactate concentrations ($p < 0.001$), and were older ($p < 0.001$). Further, these patients evidenced

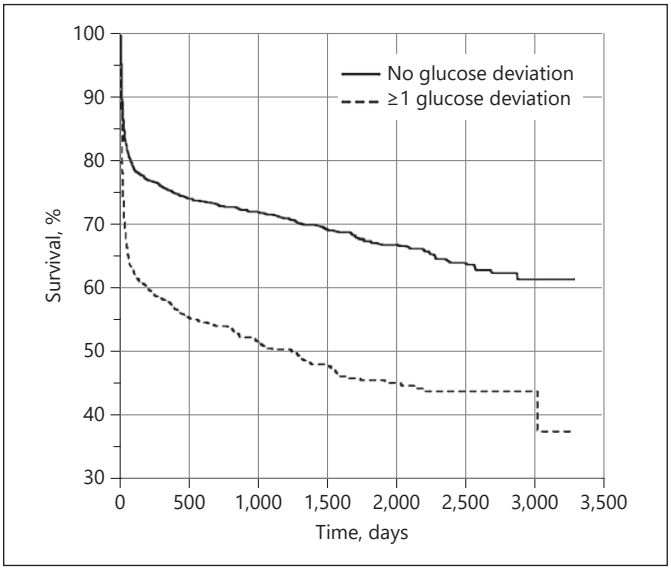

Fig. 2. A single glucose deviation was associated with adverse long-term mortality (HR 2.01; 95% CI 1.81–2.24; $p < 0.001$) compared to patients without a glucose deviation.

higher white blood count ($p < 0.001$) and laboratory signs of multiorgan failure as seen in Table 1.

Intra-ICU mortality remained associated with a single glucose deviation after correction for SAPS2 (OR 1.41; 95% CI 1.13–1.75; $p = 0.002$) and APACHE2 (OR 1.36; 95% CI 1.10–1.69; $p = 0.005$). Again, after correction in a multivariate Cox regression for either APACHE2 (HR 1.15; 95% CI 1.01–1.32; $p = 0.03$) or SAPS2 (HR 1.2; 95% CI 1.03–1.35; $p = 0.01$), a single glucose deviation re-

Table 1. Baseline characteristics and comparison of patients with and without a glucose deviation during an ICU stay

Parameter	No glucose deviation		Glucose deviation		Overall cohort		*p* value
	mean	SD	mean	SD	mean	SD	
Age, years	63.40	15.87	66.78	13.66	64.57	15.23	<0.001
Body mass index	27.00	5.08	27.67	5.66	27.26	5.32	0.002
APACHE2 score	20.94	8.96	25.22	9.35	22.65	9.35	<0.001
SAPS2	40.58	18.96	48.68	20.34	43.82	19.92	<0.001
Heart rate, bpm	100.69	23.33	107.92	24.22	103.19	23.89	<0.001
Lactate, mmol/L	2.09	2.24	3.92	4.83	2.73	3.50	<0.001
Leukocytes, $\times 10^9$/L	11.54	9.80	14.06	13.40	12.41	11.24	<0.001
Hemoglobin, mmol/L	7.63	2.68	7.60	3.48	7.62	2.98	0.74
ASAT, µmol/(L×s)	4.32	17.11	6.69	22.17	5.19	19.15	<0.001
ALAT, µmol/(L×s)	2.32	8.51	3.10	9.20	2.61	8.77	0.01
γGT, µmol/L	1.94	3.08	2.00	2.45	1.96	2.86	0.56
Bilirubin, µmol/L	24.12	42.50	26.52	46.10	24.96	43.80	0.07
Creatinine, µmol/L	156.25	155.95	185.55	155.93	166.39	156.55	<0.001
Urea, mmol/L	11.49	10.09	15.41	12.25	12.84	11.05	<0.001

ALAT, alanine aminotransferase; APACHE2, Acute Physiology and Chronic Health Evaluation II; ASAT, aspartate aminotransferase; γGT, gamma-glutamyl transferase; ICU, intensive care unit; SAPS2, Simplified Acute Physiology Score II.

Table 2. Baseline characteristics and comparison of patients with and without T2DM

Parameter	No T2DM		T2DM		*p* value
	mean	SD	mean	SD	
Age, years	63.68	15.68	70.11	10.47	<0.001
Body mass index	26.96	5.12	29.01	6.05	<0.001
APACHE2 score	22.49	9.35	23.58	9.33	0.03
SAPS2	43.54	19.94	45.48	19.80	0.07
Heart rate, bpm	103.39	24.00	101.94	23.17	0.14
Lactate, mmol/L	2.71	3.19	2.86	4.99	0.31
Leukocytes, $\times 10^9$/L	12.39	10.55	12.55	14.90	0.73
Hemoglobin, mmol/L	7.65	3.17	7.47	1.19	0.14
ASAT, µmol/(L×s)	5.20	19.09	5.07	19.51	0.89
ALAT, µmol/(L×s)	2.63	8.86	2.43	8.17	0.64
γGT, µmol/L	1.98	2.93	1.78	2.37	0.17
Bilirubin, µmol/L	25.66	45.38	20.56	31.92	0.01
Creatinine, µmol/L	163.70	156.35	183.31	156.86	0.003
Urea, mmol/L	12.53	10.93	14.81	11.58	<0.001

ALAT, alanine aminotransferase; APACHE2, Acute Physiology and Chronic Health Evaluation II; ASAT, aspartate aminotransferase; γGT, gamma-glutamyl transferase; SAPS2, Simplified Acute Physiology Score II; T2DM, type 2 diabetes.

mained to be associated with mortality in the long term in the overall cohort. A glucose deviation was associated with increased intra-ICU mortality in patients suffering from AMI (OR 3.26; 95% CI 2.19–4.87; $p < 0.001$), acute heart failure (OR 2.07; 95% CI 1.37–3.20; $p = 0.001$), and pulmonary embolism (OR 8.28; 95% CI 3.18–21.57; $p < 0.001$) as well as status post cardiopulmonary resuscitation (OR 2.88; 95% CI 1.86–4.48; $p < 0.001$) and in patients admitted for sepsis (OR 1.38; 95% CI 1.004–1.89; $p = 0.047$).

Again, in the long term a glucose deviation was associated with mortality in AMI (HR 2.48; 95% CI 1.89–3.26; $p < 0.001$), acute heart failure (HR 1.68; 95% CI 1.28–2.21;

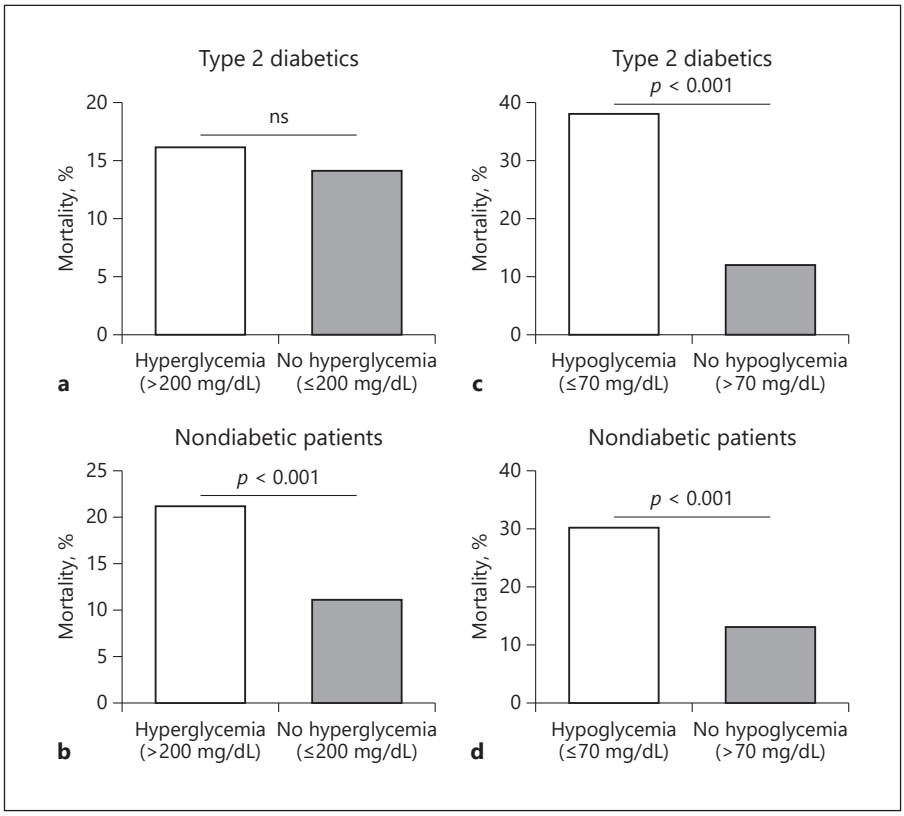

Fig. 3. a, **b** A hyperglycemic episode was not associated with increased intra-ICU mortality in patients with T2DM (21 vs. 11%; OR 2.15; 95% CI 1.79–2.57; $p < 0.001$) (**a**), but in patients without T2DM (16 vs. 14%; OR 1.05; 95% CI 0.68–1.62; $p = 0.84$) (**b**). **c**, **d** A hypoglycemic episode was associated with increased intra-ICU mortality in patients with T2DM (38 vs. 12%; OR 4.71; 95% CI 2.60–8.55; $p < 0.001$) (**c**) and without T2DM (30 vs. 13%; OR 2.94; 95% CI 2.28–3.80; $p < 0.001$) (**d**). ICU, intensive care unit; ns, nonsignificant; T2DM, type 2 diabetes.

$p < 0.001$), pulmonary embolism (HR 4.32; 95% CI 2.67–8.22; $p < 0.001$), and status post cardiopulmonary resuscitation (HR 1.73; 95% CI 1.30–2.30; $p < 0.001$) and in patients admitted for sepsis (HR 1.37; 95% CI 1.11–1.69; $p = 0.003$).

A total of 685 (14%) of our patients had a history of T2DM (Table 2). Patients suffering from T2DM were more likely to suffer from severe hyperglycemia (49 vs. 27%; $p < 0.001$), but not from hypoglycemia (8 vs. 8%; $p = 0.70$). Patients suffering from T2DM were more prone to suffer from any glucose deviation (53 vs. 32%; $p < 0.001$), and in those a glucose deviation was associated with higher mortality, both intra-ICU (16 vs. 10%; OR 1.73; 95% CI 1.10–2.73; $p = 0.02$) as well as in the long term (HR 1.48; 95% CI 1.10–1.98; $p = 0.01$). In patients suffering from T2DM, a hyperglycemic episode was neither associated with intra-ICU mortality (16 vs. 14%; OR 1.05; 95% CI 0.68–1.62; $p = 0.84$; Fig. 3a) nor with long-term mortality (HR 1.09; 95% CI 0.82–1.45; $p = 0.56$). A hypoglycemic episode was associated with both increased intra-ICU mortality (38 vs. 12%; OR 4.71; 95% CI 2.60–8.55; $p < 0.001$; Fig. 3b) and long-term mortality (HR 3.52; 95% CI 2.40–5.17; $p < 0.001$).

In patients without a history of T2DM, an episode of hypoglycemia was associated with both increased intra-ICU mortality (30 vs. 13%; OR 2.94; 95% CI 2.28–3.80; $p < 0.001$; Fig. 3d) and long-term mortality (HR 2.25; 95% CI 1.88–2.69; $p < 0.001$). An episode of hyperglycemia was associated with both increased intra-ICU mortality (21 vs. 11%; OR 2.15; 95% CI 1.79–2.57; $p < 0.001$; Fig. 3c) and long-term mortality (HR 1.81; 95% CI 1.60–2.04; $p < 0.001$). A glucose deviation was associated with intra-ICU mortality (23 vs. 10%; OR 2.87; 95% CI 2.40–3.42; $p < 0.001$) and long-term mortality (HR 2.15; 95% CI 1.91–2.42; $p < 0.001$) in patients without a history of T2DM.

Discussion

Critically ill patients suffering from a single glucose deviation (i.e., blood glucose concentration either >200 mg/dL or ≤70 mg/dL) during their ICU stay had increased mortality both intra-ICU and in the long term. Therefore, close monitoring and management of blood glucose concentration seems warranted in critically ill patients.

As patients suffering from a glucose derailment were clinically sicker in our study, glucose deviation might primarily be interpreted as a surrogate parameter for illness severity. On the other hand, after correction for both APACHE2 score and SAPS2, glucose deviation remained associated with adverse outcome. We therefore postulate that blood glucose derailment, especially hypoglycemia, might constitute an independent risk factor.

Patients suffering from diabetes were more prone to suffer from a glucose deviation, but in patients with diabetes, hyperglycemia was not associated with mortality, which might probably be due to adaptation to higher blood glucose concentrations [11, 12]. The pathophysiology of chronic hyperglycemia is different from that of acute hyperglycemia, but could make patients suffering from diabetes more resistant to acute hyperglycemic episodes during their ICU stay [21]. The fact that diabetes per se does not represent a risk factor for higher mortality in ICU patients might support this theory [28].

As hypoglycemia, even defined at a relatively liberal level of ≤70 mg/dL, was associated with mortality both in patients suffering and not suffering from diabetes, close glucose monitoring is imperative in all critically ill patients. However, it seems that certain adaptations in blood glucose management for patients suffering from diabetes might further improve outcome and prognosis. In patients with known T2DM, it seems reasonable to focus especially on prevention of hypoglycemia during the ICU stay while striving for more moderate targets regarding hyperglycemia [21]. Certainly this notion is limited by low absolute numbers of hypoglycemia in patients suffering from T2DM in our cohort, but similar to septic patients, in patients suffering from diabetes a more liberal approach to blood glucose management, focusing on avoiding fluid shifts due to osmotic disbalances, should be considered, and even blood glucose concentrations >200 mg/dL might be tolerated for a limited time [8, 25, 29]. Our results further emphasize the notion that patients with and without T2DM should be approached distinctly with regards to glucose hemostasis and management [30].

In nondiabetic, critically ill patients a more aggressive treatment goal might be warranted, and keeping blood glucose concentration ≤200 mg/dL and >70 mg/dL could further optimize our patients' outcome.

Limitations

Our study is retrospective and based on a single center. Regarding the diagnosis of diabetes, we had neither HbA1c nor oral glucose tolerance test values, but only data from medical history. Patients were treated according to the treating physician's decisions following international guidelines, but regarding glucose management there was no predefined treatment or management algorithm. More frequent laboratory controls in clinically sicker patients might make our analysis susceptible to selection bias. We do not have data about specific symptoms of hypoglycemic patients. Further, we have no data on enteral or parenteral calorie supply or insulin treatment.

Conclusion

Blood glucose concentration constitutes an important risk parameter in the critically ill, as both hyper- and hypoglycemia are associated with adverse outcome. Blood glucose concentration might need differential approaches depending on concomitant diseases, especially T2DM.

Statement of Ethics

The study was approved by the local ethics committee of the Jena University Hospital and the Medical Faculty of the Friedrich Schiller University of Jena.

Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this paper.

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