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

Bernhard Wernly\textsuperscript{a} Peter Jirak\textsuperscript{a} Michael Lichtenauer\textsuperscript{a} Marcus Franz\textsuperscript{b} Bjoern Kabisch\textsuperscript{b} Paul C. Schulze\textsuperscript{b} Kristina Braun\textsuperscript{c} Johanna Muessig\textsuperscript{c} Maryna Masyuk\textsuperscript{c} Bernhard Paulweber\textsuperscript{d} Alexander Lauten\textsuperscript{e,f} Uta C. Hoppe\textsuperscript{a} Malte Kelm\textsuperscript{c} Christian Jung\textsuperscript{c}

\textsuperscript{a}Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Salzburg, Austria; \textsuperscript{b}Clinic of Internal Medicine I, Department of Cardiology, Jena University Hospital, Jena, Germany; \textsuperscript{c}Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany; \textsuperscript{d}Clinic of Internal Medicine I, Paracelsus Medical University of Salzburg, Salzburg, Austria; \textsuperscript{e}Klinik für Kardiologie, Charité – Universitätsmedizin Berlin, Berlin, Germany; \textsuperscript{f}Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), Standort Berlin, Berlin, Germany

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...
Glucose Deviation in Critically Ill Patients

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.

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].

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.

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 Software bvba, Ostend, Belgium; www.medcalc.org; 2018) and
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 as higher long-term mortality (HR 2.01; 95% CI 1.81–2.24; p < 0.001) compared to patients without a glucose deviation.

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 higher white blood count (p < 0.001) and laboratory signs of multigorgan 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-
Glucose Deviation in Critically Ill Patients

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 1.00–1.89; \( p = 0.047 \)).

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 1.28–2.11;...
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) 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.

References

1 Hermanides J, Bosman RJ, Vriesendorp TM, Dotsch R, Rosendaal FR, Zandstra DF, et al. Hypoglycemia is associated with intensive care unit mortality. Crit Care Med. 2010 Jun; 38(6):1430–4.
2 Jung C, Kelm M. Evaluation of the microcirculation in critically ill patients. Clin Hemo- rheol Microcirc. 2015; 61(2):213–24.
3 Salluh JI, Soares M. ICU severity of illness scores: APACHE, SAPS and MPM. Curr Opin Crit Care. 2014 Oct;20(5):557–65.
4 Morales J, Schneider D. Hypoglycemia. Am J Med. 2014 Oct;127(10 Suppl):S1–7–24.
6 Tiruvoipati R, Chiezey B, Lewis D, Ong K, van Vught LA, Wiewel MA, Klein Klouwenberg P, et al. Stress hyperglycaemia may not be harmful in critically ill patients with sepsis. J Crit Care. 2012 Apr;27(2):153–8.

7 Losser MR, Dumanis C, Payen D. Bench-to-bedside review: glucose and stress conditions in the intensive care unit. Crit Care. 2010; 14(4):231.

8 van Vught LA, Wiewel MA, Klein Klouwenberg PM, Hoogendijk AJ, Scicluna BP, Ong DS, et al.; Molecular Diagnosis and Risk Stratification of Sepsis Consortium. Admission Hyperglycaemia in Critically Ill Sepsis Patients: Association With Outcome and Host Response. Crit Care Med. 2016 Jul;44(7):1338–46.

9 Kinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003 Dec;78(12):1471–8.

10 Hoebers LP, Damman P, Claessen BE, Vis MM, Baan J Jr, van Straalen JP, et al. Predictive value of plasma glucose level on admission for short and long-term mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol. 2012 Jan;109(1):53–9.

11 Dugan LL, You YH, Ali SS, Diamond-Stanic M, Miyamoto S, DeCleves AE, et al. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. J Clin Invest. 2013 Nov;123(11):4888–99.

12 Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001 Dec;414(6865):813–20.

13 Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar;360(13):1283–97.

14 Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009 Oct;35(10):1738–48.

15 De La Rosa GC, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, et al.; Grupo de Investigacion en Cuidado intensivo: GICl-HPTU. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Crit Care. 2008;12(5):R120.

16 De Block CE, Rogiers P, Jorens PG, Schepens T, Scuffi C, Van Gaal LF. A comparison of two insulin infusion protocols in the medical intensive care unit by continuous glucose monitoring. Ann Intensive Care. 2016 Dec;6(1):115.

17 Lacherade JC, Jacqueminet S, Preiser JC. An overview of hypoglycaemia in the critically ill. J Diabetes Sci Technol. 2009 Nov;3(6):1242–9.

18 Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of the critically ill? Diabetologia. 2006 Aug;49(8):1722–5.

19 Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes – the “dead in bed” syndrome revisited. Diabetologia. 2009 Jan;52(1):42–5.

20 Park S, Kim DG, Suh GY, Kang JG, Ju YS, Lee YJ, et al. Mild hypoglycemia is independently associated with increased risk of mortality in patients with sepsis: a 3-year retrospective observational study. Crit Care. 2012 Oct;16(5):R189.

21 Siegelaar SE, Hoekstra JB, DeVries JH. Special considerations for the diabetic patient in the ICU: targets for treatment and risks of hypoglycaemia. Best Pract Res Clin Endocrinol Metab. 2011 Oct;25(5):825–34.

22 Hoang QN, Pisani MA, Inzucchi S, Hu B, Honiden S. The prevalence of undiagnosed diabetes mellitus and the association of baseline glycemic control on mortality in the intensive care unit: a prospective observational study. J Crit Care. 2014 Dec;29(6):1052–6.

23 Jung C, Rafnsson A, Shemyakin A, Böhm F, Pernow J. Different subpopulations of endothelial progenitor cells and circulating apoprotic progenitor cells in patients with vascular disease and diabetes. Int J Cardiol. 2010 Sep;143(3):368–72.

24 Pernow J, Jung C. The Emerging Role of Arginine in Endothelial Dysfunction in Diabetes. Curr Vasc Pharmacol. 2016;14(2):155–62.

25 Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig J, Masyuk M, et al. Differential Impact of Hyperglycemia in Critically Ill Patients: Significance in Acute Myocardial Infarction but Not in Sepsis? Int J Mol Sci. 2016 Sep;17(9):E1586.

26 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993 Dec;270(24):2957–63.

27 Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med. 1981 Aug;9(8):591–7.

28 Bannier K, Lichtenauer M, Franz M, Fritzenwanger M, Kabisch B, Figulla HR, et al. Impact of diabetes mellitus and its complications: survival and quality-of-life in critically ill patients. J Diabetes Complications. 2015 Nov-Dec;29(8):1130–5.

29 Wernly B, Lichtenauer M, Hoppe UC, Jung C. Hyperglycemia in septic patients: an essential stress survival response in all, a robust marker for risk stratification in some, to be messed with in none. J Thorac Dis. 2016 Jul;8(7):E621–4.

30 Kinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care. 2013 Mar;17(2):R37.