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Updates in Glycemic Management in the Hospital

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Abstract

Purpose of Review To provide an update of glycemic management during metabolic stress related to surgery or critical illness.

Recent Findings There is a clear association between severe hyperglycemia, hypoglycemia, and high glycemic variability and poor outcomes of postoperative or critically ill patients. However, the impressive beneficial effects of tight glycemic management (TGM) by intensive insulin therapy reported in one study were never reproduced. Hence, the recommendation of TGM is now replaced by more liberal blood glucose (BG) targets (< 180 mg/dL or 10 mM). Recent data support the concept of targeting individualized blood glucose (BG) values according to the presence of diabetes mellitus/chronic hyperglycemia, the presence of brain injury, and the time from injury.

Summary A more liberal glycemic management goal is currently advised during metabolic stress and could be switched to individualized glycemic management once validated by prospective trials.

Keywords Stress hyperglycemia · Insulin resistance · Critically ill · Postoperative care · Insulin · Glucose

Introduction

Hyperglycemia, previously called "diabetes of injury", is considered as a physiological component of the stress response [1]. The era of blood glucose (BG) management in critically ill patients began in the late 1980s, when cardiac surgeons started treating diabetes patients with insulin and demonstrated, over time, reductions in mortality and infection rates as well as cost of care [2]. A landmark trial published in 2001 in the New England Journal of Medicine (NEJM) revealed the startling results of the Leuven I study [3]. This investigation compared two intensive care unit (ICU) insulin regimens, with an intensive group (BG target 80–110 mg/dL) or a control group representative of usual care (BG target below 200 mg/dL). A 4% decrease in the absolute mortality of critically ill patients randomized to intensive insulin therapy (ITT) was found. These results triggered much enthusiasm and supported recommendations to implement tight glucose management (TGM) by IIT in ICUs by several US health care agencies (Joint Commission on Accreditation of Healthcare Organization, the Institute for Healthcare Improvement, and the Voluntary Hospitals of America (VHA)) [4].

Since 2001, other investigators tried to reproduce the Leuven results and examine the underlying mechanisms of the findings of the Leuven team, in intensive care units [5–12], stroke centers or neurointensive care units [13–15], coronary care units [16], or liver transplant centre [17]. Overall, the results of the Leuven I study were never reproduced, as the mortality rate did not decrease in patients randomized to TGM, as compared to a more liberal target. The rate of hypoglycemia was uniformly increased in the groups randomized to TGM. The largest trial, i.e., Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR study), showed a significant increase in 90-day mortality in patients who received intensive treatment with insulin [5], in part related to an increased rate of hypoglycemia [18]. A systematic review and network meta-analysis of 36 randomized controlled trials (n = 17,996 patients) showed no mortality benefit of TGM, but a 5-fold increase in the rate of hypoglycemia. Among numerous

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hypotheses suggested to explain the discrepancies between the results of the Leuven I and the other studies, the lack of achievement of the predefined BG target in several studies and the confounding effect of the intravenous infusion of large amounts of glucose in Leuven, and not in the other centers are usually quoted.

In patients who underwent scheduled surgical procedures, some beneficial effects of TGM have been reported, mainly in terms of decrease of infectious complications [19•, 20•]. Specifically, the first meta-analysis [21•] reported a benefit or TGM in terms of infection rate, as compared to the standards of care used in 15 studies ($n = 5053$ patients). The second meta-analysis [22] reported decreased risks of short-term mortality (26 trials, $n = 9315$). Importantly, the patients randomized to the "TGM" arm were treated to achieve a varying target range (upper limit from 110 up to 150 mg/dL). Importantly, the positive results of these meta-analyses were mainly driven by the data of the Leuven I study, which was performed in a surgical ICU. Furthermore, the target BG in the patients randomized to the TGM arm of the individual studies varied over a wide range, with an upper limit from 110 to 180 mg/dL. In a recent systematic Cochrane review [22], TGM was not associated with a consistent improvement of surgical site infection. Hence, no consistent benefit of TGM was found in postoperative patients.

Thus, these different results from RCTs performed in critically ill and postoperative patients yielded inconsistent results, raise several uncertainties, and support the need for further clinical research [23]. This review aims to summarize (1) the new insights of stress hyperglycemia in the inpatient setting, (2) the most recent clinical findings in selected groups of patients, and (3) the evolution of recommendations for clinical practice.

Stress Hyperglycemia: New Insights

Prevalence and Definition

Stress hyperglycemia (SH) is a common metabolic response occurring in the critically ill, following trauma or surgery, even in the absence of diabetes mellitus. Its prevalence ranges from 20 to 75% in critically ill patients according to the threshold value used [24•]. Indeed, the presence of a BG value > 110 mg/dL was used to define SH in some studies, while higher thresholds were used in other studies [24•]. Hence, the major differences in the incidence of SH reflect partially the wide ranges of definitions. In the past, "Hospital-related hyperglycemia" was defined as any fasting BG > 124 mg/dL or a random BG glucose > 200 mg/dL during a hospital stay, which reverts to normal after discharge [1]. In 2017, The American Diabetes Association proposed a new definition of SH as transient hyperglycemia in a patient with no history of diabetes with an acute illness or that has undergone an invasive procedure (surgery or others) [25, 26•]. It is characterized by blood-glucose levels ≥ 180 mg/dL with levels returning to normal (< 126 mg/dL) after removal of the stressor and withdrawal of glucose-lowering treatment, if it was started previously in a patient whose HbA1c was < 6.5% .

Further studies should rely on a uniform definition in order to enable comparisons between studies and a more thorough assessment of performance and quality of GM. The ability to achieve a pre-defined target BG must be reported, according to unifying metrics, such as time in the target range [23].

Pathophysiology

The pathophysiology behind "stress hyperglycemia" is complex and comprises merely insulin resistance, an adaptive component during the acute phase of critical illness. The elaboration of glucose, primarily by the liver, is known to be an essential component of the host response to injury [26•]. The supply of glucose to injured tissues is concentration-dependent and mostly insulin-independent. The provision of large amounts of glucose is hence required and depends on hepatic gluconeogenesis, itself driven primarily by the direct action of glucagon, epinephrine, cortisol, and inflammatory cytokines [4, 27].

Clinically, a moderate hyperglycemia could hence be considered as desirable [28]. An aggressive treatment aiming at the achievement of "normoglycemia" could be inappropriate, but also lowers BG below a desirable value during the acute phase of the disease, when insulin resistance develops as a way to provide efficient energy substrates to life-sustaining tissues and will increase the risks of hypoglycemia [29]. In fact, insulin resistance is a hallmark of any severe injury [29, 30] and has evolved as mechanism designed to promote the survival of any living body by the provision of neoglucogenic substrates [31]. In surgical patients, perioperative insulin resistance may last for several days. Importantly, modifiable factors such as the duration of the surgical procedure, the amount of perioperative blood loss, prolonged immobilization, and fasting can further enhance insulin resistance, which is of course unnecessary and possibly detrimental on a long-term basis [26•].

Besides insulin resistance, other mechanisms have been involved, including an uncontrolled glucagon release under the effect of catecholamines or adrenal hormones [32]. Likewise, a blunting of the incretin effect has been reported in the critically ill [33, 34], thereby leading to an insufficient insulin secretion. Finally, a single-nucleotide polymorphism (rs7903146) of the transcription factor 7-like 2 gene (TCF7L2) could influence the insulin response in case of stress, as its transcription induces the insulin secretion by pancreatic β cells and is involved in the susceptibility to develop type 2 diabetes [35•]. This genetic predisposition to develop

stress hyperglycemia has been suspected but not confirmed in a large study performed on 991 critically ill patients [36•].

Most Recent Clinical Findings

Even though an association between each domain of dysglycemia (hyperglycemia, hypoglycemia, and increased glycemic variability) and a poor outcome has been confirmed by several analyses of large cohorts [37–39], new analyses provide insightful evidence:

- The correlation between hyperglycemia and poor outcome is mostly observed in case of concomitant hyperlactatemia
- Diabetes status/chronic hyperglycemia modulates the relationship between dysglycemia and outcome
- Brain-injured patients are more susceptible to hypoglycemia than other categories of acutely ill patients, as a result of the decreased ability of the injured brain to use alternative substrates.

Association Between Hyperlactatemia and Hyperglycemia

At least three large cohort studies [40–42] reported similar findings, e.g., the presence of hyperlactatemia modulates the relationship between hyperglycemia and mortality. Physiologically, these consistent findings suggest that the toxicity of glucose is amplified when the ability to oxidize glucose is overwhelmed, as suggested by hyperlactatemia. From clinical standpoint, the BG target could differ according to the lactate concentration.

Diabetes Status/Chronic Hyperglycemia Modulates the Relation Between Dysglycemia and Outcome

The relationship between mean BG during ICU stay and mortality is distinctly different when comparing patients with and without diabetes. In patients with DM, there is a "blunted", or even absent relationship between mean BG above 80–110 mg/dL and mortality [39, 43, 44, 45•]. None of the RCT of TGM reported the relationship between mean glycemia, in distinct bands, and mortality, either for the entire cohort, or stratified by DM status. A post hoc analysis of the Leuven trials [46] reported a lack of benefit of TGM in the subset of patients with diabetes, unlike the other subgroups of patients. Likewise, the association between BG and outcomes was less pronounced in patients with diabetes than in patients without diabetes with acute myocardial infarction [47, 48]. Very recently, the relationship between diabetes status and outcome in patients with sepsis or acute bacteremia was evaluated in a retrospective cohort study of 128,222 patients admitted with sepsis over a 5-year period to 83 Dutch ICUs [45•]. Among patients with DM, only hypoglycemia in the absence of severe hyperglycemia was independently associated with risk of death. Recently published work suggests that the independent association of hypoglycemia with death may be even stronger in patients with DM than in those without [49•]. A recent cohort study including 90,644 patients of whom 5127 had an insulin-treated DM [50•] reported that patients with insulin-treated DM had lower adjusted hospital mortality with higher peak BG levels while those without DM had increased mortality with higher peak BG. For patients without DM, increasing glucose variability was associated with increased risk of death; in contrast, there was no association between increasing glucose variability and risk of death for patients with insulin treated DM.

The presence of chronic hyperglycemia is probably a key confounder in the relationship between hyperglycemia and outcomes. Egi and coworkers evaluated the relationship between acute and chronic glycemia in 415 patients with DM admitted to 2 Australian ICUs [51]. Chronic glycemia was characterized by glycated hemoglobin (HbA1c) levels obtained on admission. There was no significant difference in mean BG or mean HbA1c levels between survivors and non-survivors. However, for patients with low HbA1c levels, increasing mean ICU dysglycemia was associated with increased risk of death, and for patients with high HbA1c levels, low mean ICU dysglycemia was associated with increased risk of death. This landmark study suggested that for patients who achieved glycemic targets prior to admission, reflected by in range HbA1c levels, the relationship between mean ICU glycemia and mortality was similar to that seen among patients without DM, and that for patients with above range A1cs prior to admission, higher BG targets may be reasonable and appropriate. More recently, Roberts et al. [52] calculated in a group of 2290 patients acutely admitted to a tertiary hospital the stress hyperglycemia ratio (admission BG/estimated average BG deducted from admission HbA1c) and found in a multivariable analysis, that the association between the stress hyperglycemia ratio and poor outcomes was maintained. We recently reported similar findings in a sample of 311 consecutive admissions [53].

In another recent single-center 1000 patient study (22% with previously diagnosed diabetes), peak dysglycemia during the first 48 h of admission was associated with mortality, stratified by the patient's HgbA1c level upon admission [54].

Altogether, these findings suggest that target BG should be calculated according to the estimated average BG level. A recent "before and after" study confirms the relevance of this approach, when the observed-to-expected mortality decreased as BG target was changed to a higher level in patients with diabetes [55•].

Brain-Injured Patients Are More Susceptible to Hypoglycemia than Other Categories of Acutely Ill Patients

Brain-injured patients are particularly sensible to variations in BG, as a result of the limited glucose reserves, and the requirement of energy substrates. Conversely, hypoglycemia can further impair cerebral dysfunction and hence must be avoided in brain-injured patients. On the other hand, severe hyperglycemia is also associated with a worsening of brain dysfunction, as reported by various observational studies performed in patients with traumatic brain injury (TBI) and intracerebral hemorrhage [56, 57•]. Several prospective trials have compared "tight" versus "conventional" glucose management protocols in patients in neuro-ICUs for an acute cerebral insult [58, 59]. These studies reported increased rates of hypoglycemia in patients in the TGM group with little or no impact on mortality or neurological outcomes. The traditional cutoff values used to define hypoglycemia may need to be reconsidered in these patients, in view of the negative impact of mild-to-moderate hypoglycemia on secondary brain injury.

In a retrospective analysis, Meier et al. reported that a BG target of 63–117 mg/dL during the first week in patients with TBI was associated with significantly elevated intracranial pressure and a trend toward increased mortality compared to a target of 90–144 mg/dL, whereas in the second week, the lower target seemed more beneficial [60]. It may therefore be that glucose concentrations should be kept at higher levels during the early phase of TBI, and possibly other acute neurologic conditions, and lower targets used at later stages [61].

Evolution of Recommendations for Clinical Practice

After the initial enthusiasm for TGM and recommendations issued by The Joint Commission (https://www.jointcommission.org), the Institute for Healthcare Improvement (http://www.ihi.org/), and Vizient (formerly known as Voluntary Hospitals of America, https://www.vizientinc.com/), the pendulum swung in the opposite direction after the publication of the negative trials. The American Diabetes Association Standards of Medical Care (2019) [62] recommends that in hospitalized patients, insulin therapy should be started for persistent hyperglycemia (BG ≥ 180 mg/dL) and BG should be targeted at 140–180 mg/dL for most critically ill and non-critically ill patients after an initiation of insulin therapy. More stringent goals, such as 110–140 mg/dL (BG 110–140 mg/dL), may be appropriate in selected patients as long as it can be achieved without significant hypoglycemia (BG ≤ 70 mg/dL). For patients on intravenous insulin therapy, more frequent BG monitoring is recommended, ranging from every 30 to 120 min in order to titrate the infusion rate of the insulin drip and avoid hypo and hyperglycemia. This target BG can be applied in patients undergoing surgery [63•]. Similarly, regardless of precise value, expert consensus in European guidelines [64] recommend a target BG of less than 180 mg/dL and to avoid "tight" glucose management (BG 80–110 mg/dL) in emergency situations in adult ICU patients without diabetes. Additionally, they suggested to avoid marked glucose variability and to restrict intravenous glucose infusions in cases of hyperglycemia.

Conclusion

The management of stress hyperglycemia should be individualized in order to achieve BG targets according to patient-related factors such as the presence of diabetes/chronic hyperglycemia, or brain injury. Likewise, time-related factors could also modulate the BG target range, such as the magnitude of insulin resistance and the presence of hyperlactatemia. Computer-assisted closed-loops linking continuous monitoring devices to automated insulin infusion pumps could be beneficial in the future to achieve safe and effective predefined BG targets [23, 65].

Compliance with Ethical Standards

Conflict of Interest Wasineenart Mongkolpun and Bruna Provenzano declare that they have no conflict of interest.

Jean-Charles Preiser reports personal fees from Optiscan, Edwards Lifesciences, and Medtronic.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373:1798–807.
2. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2003;125:1007–21.
3. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
4. Preiser J (2010) 72 - Should Blood Glucose Be Tightly Controlled in the Intensive Care Unit? In: Deutschman CS, Neligan PJ (eds) Evidence-Based Practice of Critical Care. Saunders, Philadelphia, an imprint of Elsevier Inc., pp 505–508

5. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
6. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.
7. De La Rosa GD, Donado JH, Restrepo AH, et al. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Crit Care. 2008;12: R120.
8. Arabi Y, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36:3190–7.
9. Kalfon P, Giraudeau B, Ichai C, et al. Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial. Intensive Care Med. 2014;40:171–81.
10. COIITSS Study Investigators, Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA. 2010;303: 341–8.
11. Brunkhorst FM, Engel C, Bloos F, German competence network Sepsis (SepNet), et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
12. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomized multi-Centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35:1738–48.
13. Rosso C, Corvol JC, Pires C, Crozier S, Attal Y, Jacqueminet S, et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized INSULINFARCT trial. Stroke. 2012;43:2343–9.
14. Bilotta F, Spinelli A, Giovannini F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol. 2007;19:156–60.
15. Bilotta F, Caramia R, Paoloni FP, et al. Safety and efcacy of intensive insulin therapy in critical neurosurgical patients. Anesthesiology. 2009;110:611–9.
16. de Mulder M, Umans VA, Cornel JH, et al. Intensive glucose regulation in hyperglycemic acute coronary syndrome: results of the randomized BIOMarker study to identify the acute risk of a coronary syndrome-2 (BIOMArCS-2) glucose trial. JAMA Intern Med. 2013;173:1896–904.
17. Wallia A, Schmidt K, Oakes DJ, et al. Glycemic control reduces infections in post-liver transplant patients: results of a prospective, Randomized Study. J Clin Endocrinol Metab. 2017;102:451–9.
18. The NICE-SUGAR. Study investigators hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367:1108–18.
19.• Wang YY, Hu SF, Ying HM, Chen L, Li HL, Tian F, et al. Postoperative tight glycemic control significantly reduces postoperative infection rates in patients undergoing surgery: a meta-analysis. BMC Endocr Disord. 2018;18:42. **An updated systematic review on the effect of tight glycemic control on postoperative infections.**
20.• Kang ZQ, Huo JL, Zhai XJ. Effects of perioperative tight glycemic control on postoperative outcomes: a meta-analysis. Endocr Connect. 2018;7:R316–27. **An updated systematic review on the effect of tight glycemic control on postoperative complications.**
21.• Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med. 2017;43:1–15. **An important comprehensive analysis of the available clinical data on tight glycemic control in intensive care medicine.**
22. Kao LS, Meeks D, Moyer VA, Lally KP. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. Cochrane Database Syst Rev. 2009;3:CD006806.
23. Preiser JC, Chase JG, Hovorka R, et al. Glucose control in the ICU: a continuing story. J Diabetes Sci Technol. 2016;10:1372–81.
24.• Olariu E, Pooley N, Danel A, Miret M, Preiser JC. A systematic scoping review on the consequences of stress-related hyperglycaemia. PLoS One. 2018;13:e0194952. **A systematic review of the available data on the associations between hyperglycemia and outcomes in the critically ill.**
25. American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care. 2017;40(Suppl. 1):S11–24.
26.• Cheisson G, Jacqueminet S, Cosson E, et al. Perioperative management of adult diabetic patients. Review of hyperglycaemia: definitions and pathophysiology. Anaesth Crit Care Pain Med. 2018;37(Suppl 1):S5–8. **A practical and updated approach of the management of diabetes before and after surgery.**
27. Preiser JC, Ichai C, Orban JC, Groeneveld AB. Metabolic response to the stress of critical illness. Br J Anaesth. 2014;113:945–54.
28. Preiser JC. Restoring normoglycaemia: not so harmless. Crit Care. 2008;12:116.
29. Lena D, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. Anesthesiology. 2011;114:438–44.
30. Uyttendaele V, Dickson JL, Shaw GM, Desaive T, Chase JG. Untangling glycaemia and mortality in critical care. Crit Care. 2017;21:152.
31. Soeters MR, Soeters PB. The evolutionary benefit of insulin resistance. Clin Nutr. 2012;31:1002–7.
32. Harp JB, Yancopoulos GD, Gromada J. Glucagon orchestrates stress-induced hyperglycaemia. Diabetes Obes Metab. 2016;18: 648–53.
33. Nielsen ST, Janum S, Krogh-Madsen R, Solomon TP, Møller K. The incretin effect in critically ill patients: a case-control study. Crit Care. 2015;19:402.
34. Jamaludin UK, Docherty PD, Chase JC, et al. Observation of incretin effects during enteral feed transitions of critically ill patients. e-SPEN J. 2012;7:e154–9.
35.• Ding W, Xu L, Zhang L, et al. Meta-analysis of association between TCF7L2 polymorphism rs7903146 and type 2 diabetes mellitus. BMC Med Genet. 2018;19:38. **A systematic review of the association studies confirming the presence of a single polymorphism as a risk factor for type 2 diabetes mellitus across all ethnicities.**
36.• Ben Hamou A, Kipnis E, Elbaz A, et al. Association of transcription factor 7-like 2 gene (TCF7L2) polymorphisms with stress-related hyperglycaemia (SRH) in intensive care and resulting outcomes: The READIAB study. Diabetes Metab. 2019; **A large-scale study assessing the presence of a single polymorphism as a risk factor for stress hyperglycemia**. https://doi.org/10.1016/j.diabet.2019.05.001.
37. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med. 2012;40:3180–8.
38. Falciglia M, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37: 3001–9.
39. Krinsley JS, Egi M, Kiss A, 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;17:R37.
40. Green JP, Berger T, Garg N, et al. Hyperlactatemia affects the association of hyperglycemia with mortality in nondiabetic adults with sepsis. Acad Emerg Med. 2012;19:1268–75.
41. Kaukonen KM, Bailey M, Egi M, Orford N, Glassford NJ, Marik PE, et al. Stress hyperlactatemia modifies the relationship between

stress hyperglycemia and outcome: a retrospective observational study. Crit Care Med. 2014;42(6):1379–85.
42. Freire Jorge P, Wieringa N, de Felice E, van der Horst ICC, Oude Lansink A, Nijsten MW. The association of early combined lactate and glucose levels with subsequent renal and liver dysfunction and hospital mortality in critically ill patients. Crit Care. 2017;21:218.
43. Egi M, Bellomo R, Stachowski E. Etal. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36:2249–55.
44. Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM, et al. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. Crit Care. 2013;17:R52.
45.• van Vught LA, Holman R, de Jonge E, et al. Diabetes is not associated with increased 90-day mortality risk in critically ill patients with sepsis. Crit Care Med. 2017;45:e1026–35. **Analysis of a national database showing differences between the associations of dysglycemia and outcomes according to the presence of diabetes.**
46. Van den Berghe G, Wilmer A, Milants I. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55:3151–9.
47. Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek EP, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation. 2005;111:3078–86.
48. Mesotten D, Preiser JC, Kosiborod M. Glucose management in critically ill adults and children. Lancet Diabetes Endocrinol. 2015;3:723–33.
49.• Egi M, Krinsley JS, Maurer P, et al. Pre-morbid glycemic control modifies the interaction between acute hypoglycemia and mortality. Intensive Care Med. 2016;42:562–71. **Multinational multicenter observational study showing differences between the associations of dysglycemia and outcomes according to the admission HbA1c level.**
50.• Magee F, Bailey M, Pilcher DV, Mårtensson J, Bellomo R. Early glycemia and mortality in critically ill septic patients: Interaction with insulin-treated diabetes. J Crit Care. 2018;45:170–7. **Analysis of a large database of septic patients showing different relationship between hospital mortality and highest glucose levels and glycemic variability in the first 24 h, according to the presence of insulin-treated diabetes.**
51. Egi M, Bellomo R, Stachowski E, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med. 2011;39:105–11.
52. Roberts GW, Quinn SJ, Valentine N. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab. 2015;100:4490–7.
53. Preiser JC, Lheureux O, Prevedello D. A step toward personalized glycemic control. Crit Care Med. 2018;46:1019–20.
54. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014;40:973–80.
55.• Krinsley JS, Preiser JC, Hirsch IB. Safety and efficacy of personalized glycemic control in critically ill patients: a 2-year before and after interventional trial. Endocr Pract. 2017;23:318–30. **A proof-of concept clinical investigation showing an improvement of survival when a higher blood glucose target was applied in patients with chronic hyperglycemia.**
56. Bosarge PL, Shoultz TH, Griffin RL, Kerby JD. Stress-induced hyperglycemia is associated with higher mortality in severe traumatic brain injury. J Trauma Acute Care Surg. 2015;79:289–94.
57.• Saxena A, Anderson CS, Wang X, et al. Prognostic Significance of Hyperglycemia in Acute Intracerebral Hemorrhage: The INTERACT2 Study. Stroke. 2016;47:682–8. **Analysis of a large cohort of patients with intracerebral hemorrhage enrolled in an interventional trial on blood pressure management, showing an association between admission hyperglycemia, diabetes mellitus and poor nerological outcome.**
58. Green DM, O'Phelan KH, Bassin SL, Chang CW, Stern TS, Asai SM. Intensive versus conventional insulin therapy in critically ill neurologic patients. Neurocrit Care. 2010;13:299–306.
59. Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. Anesthesiology. 2009;110:611–9.
60. Meier R, Béchir M, Ludwig S, et al. Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/l versus 5 to 8 mmol/l) in patients with severe traumatic brain injury. Crit Care. 2008;12:R98.
61. Lheureux O, Prevedello D, Preiser JC. Update on glucose in critical care. Nutrition. 2019;59:14–20. https://doi.org/10.1016/j.nut.2018.06.027.
62. American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S173–81.
63.• Cosson E, Catargi B, Cheisson G, Jacqueminet S, Ichai C, Leguerrier AM, et al. Practical management of diabetes patients before, during and after surgery: A joint French diabetology and anaesthesiology position statement. Diabetes Metab. 2018;44(3):200–16. **A practical and updated approach of the management of diabetes before and after surgery.**
64. Ichai C, Preiser JC, Société Française d'Anesthésie-Réanimation, Société de Réanimation de langue Française, & Experts group. International recommendations for glucose control in adult non diabetic critically ill patients. Crit Care. 2010;14(5):R166.
65. Leelarathna L, English SW, Thabit H, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. Crit Care. 2013;17:R159.