A systematic scoping review on the consequences of stress-related hyperglycaemia

Elena Olariu¹, Nicholas Pooley¹, Aurélie Danel², Montserrat Miret², Jean-Charles Preiser³*

¹ PHMR Ltd, London, United Kingdom, ² Nestlé Health Science, Vevey, Switzerland, ³ Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

* Jean-Charles.Preiser@erasme.ulb.ac.be

Abstract

Background
Stress-related hyperglycaemia (SHG) is commonly seen in acutely ill patients and has been associated with poor outcomes in many studies performed in different acute care settings. We aimed to review the available evidence describing the associations between SHG and different outcomes in acutely ill patients admitted to an ICU. Study designs, populations, and outcome measures used in observational studies were analysed.

Methods
We conducted a systematic scoping review of observational studies following the Joanna Briggs methodology. Medline, Embase, and the Cochrane Library were searched for publications between January 2000 and December 2015 that reported on SHG and mortality, infection rate, length of stay, time on ventilation, blood transfusions, renal replacement therapy, or acquired weakness.

Results
The search yielded 3,063 articles, of which 43 articles were included (totalling 536,476 patients). Overall, the identified studies were heterogeneous in study conduct, SHG definition, blood glucose measurements and monitoring, treatment protocol, and outcome reporting. The most frequently reported outcomes were mortality (38 studies), ICU and hospital length of stay (23 and 18 studies, respectively), and duration of mechanical ventilation (13 studies). The majority of these studies (40 studies) compared the reported outcomes in patients who experienced SHG with those who did not. Fourteen studies (35.9%) identified an association between hyperglycaemia and increased mortality (odds ratios ranging from 1.13 to 2.76). Five studies identified hyperglycaemia as an independent risk factor for increased infection rates, and one identified it as an independent predictor of increased ICU length of stay.

Discussion
SHG was consistently associated with poor outcomes. However, the wide divergences in the literature mandate standardisation of measuring and monitoring SHG and the creation
of a consensus on SHG definition. A better comparability between practices will improve our knowledge on SHG consequences and management.

Introduction

Hyperglycaemia is frequently observed in critically ill patients [1] and can occur in the absence of pre-existing glucose intolerance or diabetes mellitus. In critical illness, hyperglycaemia appears to be the result of stress, hence its denomination of stress-related hyperglycaemia (SHG). However, there is currently no universal threshold for the definition of SHG [2], yielding very different estimates of its prevalence (from 19.9% when blood glucose (BG) levels were higher than 153 mg/dL (8.5 mmol/L) [3] to 75% when the threshold was 110 mg/dL (6.1 mmol/L) [4]).

Regardless of its prevalence, several studies have shown that SHG is associated with complications, prolonged stay in intensive care units (ICUs) and hospitals, increased incidence of infection, increased mortality, and increased use of resources [5–9]. In survivors of critical illness, an association between SHG during hospitalisation and subsequent diabetes has been shown in several studies [10–14], with patients with SHG having an increased risk of incident diabetes [13].

However, the optimal management of SHG is still unknown, as prospective interventional studies targeting predefined BG levels with insulin yielded highly conflictual results. In a single-centre interventional trial conducted in 2001, Van den Berghe and colleagues showed the benefits of treating SHG with intensive insulin therapy and its direct clinical implications in ICU patients. Reduced morbidity (bloodstream infections, acute renal failure requiring dialysis, red-cell transfusions, ICU-acquired weakness) and mortality were observed in surgical ICU patients whose target BG levels were 80–110 mg/dL (4.4–6.1 mmol/L) [4]. Subsequently, other interventional trials were unable to reproduce the results of the pioneering trial [15–21]; for example, the NICE-SUGAR study found that a target BG level of <180 mg/dL was associated with a reduced 90-day mortality rate compared with 81–108 mg/dL [22]. Similarly, the Glucontrol study did not demonstrate a difference in mortality between patients randomised to a target BG range of 79.2–111.6 mg/dL and 140.4–180 mg/dL [23]. Therefore, there is a lack of external validation of the target BG levels observed in previous trials and no widely accepted SHG definition. This is both a result of heterogeneous patient characteristics and management and divergence in individual study design, including BG target, type of BG measurement, outcome variable (e.g. 28-, 90-, or 180-day mortality, or ICU or hospital mortality), setting, and available resources [24]. The published systematic reviews and meta-analyses pooled highly heterogeneous data [24–26].

Hence, a clearer view is urgently needed (1) to better characterize a clinically relevant and widely acceptable definition of SHG and (2) to allow better identification of the type of patients and situations in which SHG is associated with a poor outcome, and in whom therapeutic strategies of SHG should be assessed. This may require a flexible approach in which SHG is not absolutely defined for all patients, but can be adapted according to the type of patient and their circumstances. It should also be noted that SHG is not the same as high blood glucose levels, which may resolve without the need for treatment. Better SHG definitions will allow patients requiring SHG treatment to be more clearly identified. This systematic scoping review aimed to provide a basis for these more targeted research questions from observational data of hyperglycaemia in the acutely ill patient.
Methods
The Joanna Briggs Institute guidelines on conducting systematic scoping reviews were followed [27–29]. This methodology summarizes the evidence available on a topic in order to convey the breadth and depth of that topic.

Research question
The research question for this review was: ‘What are the characteristics, breadth, and results of the existing research conducted in observational settings on the clinical burden of hyperglycaemia in acutely ill adult patients admitted to ICUs?’

Information sources and search strategy
A search strategy combining both MeSH and free-text terms for hyperglycaemia and ICU settings was developed to retrieve articles of interest in the following databases: Medline; Medline In-Process Citations & Daily Update; Embase; and the Cochrane Library. The search strategy was designed in Medline and Medline In-Process and then translated to the other databases (S1 Table).

Searches were limited to English language studies and the period between January 2000 and December 2015. Additionally, publications were excluded electronically if they were indexed as case reports, case series, editorials, or letters. In addition to the electronic searches, the 2014 and 2015 proceedings of nine conferences were screened (S2 Table).

Eligibility criteria
Studies were included irrespective of the definition of SHG, if they were observational and reported data in adult patients (≥18 years) in mixed and trauma ICUs on hyperglycaemia and either of the following outcomes: mortality, infections, hospital/ICU length of stay, time on ventilation, ICU-acquired weakness, blood transfusions, and renal replacement therapy. Reviews, systematic reviews, and studies with fewer than ten hyperglycaemic patients were excluded, as were studies that compared the performance of different insulin protocols.

Study selection process
Titles and abstracts were screened by three reviewers against the agreed inclusion and exclusion criteria. Disagreements between reviewers were resolved by consensus and the reasons for exclusion were recorded only at the full-text stage.

Charting the data
The research team developed a data extraction tool that included the following items:

- article identifiers (authors, year of publication, objective)
- study identifiers (sample size, design, country, length of follow-up, inclusion and exclusion criteria)
- setting and population (age, gender, co-morbidities, reason for admission, Acute Physiology and Chronic Health Evaluation [APACHE] severity scores)
- method of BG measurement, insulin protocols, hyperglycaemia treatment protocols, definition of hyperglycaemia
• outcome measures: mortality, infections, ICU and hospital length of stay, time on mechanical ventilation, blood transfusions, renal replacement therapy, and ICU-acquired weakness.

• Data were extracted by one team member and verified by a second reviewer.

Collating, summarising, and reporting the results

A descriptive numerical summary of the characteristics of the included studies was performed. Tables and graphs were created to reflect the overall number of studies included, study designs and settings, publication years, the characteristics of the study populations, the outcomes reported, and the countries where the studies were conducted. In line with scoping reviews' methodology, an assessment of the quality of the included studies was not performed.

Results

Studies' characteristics

A total of 3,063 articles were retrieved. After title and abstract screening, 385 records were kept for full-text retrieval and 43 articles were included at full-text review (Fig 1). The results presented here are for 42 studies (536,476 patients), as two articles [30,31] were linked and reported data from the same study.

**Setting.** The reported data were mostly collected in the USA (Table 1), the commonest ICU type was trauma; however, there were more patients included in studies from mixed ICU. Trauma ICUs comprised general trauma and more specialist centres; aside from general ICUs, the most frequently reported centres cared for patients with head/brain/neurological injury, while one study reported data from a burn and trauma unit and another described patients with orthopaedic trauma (Table 1).

**Blood glucose.** Several BG thresholds were used to define SHG, ranging from 100 mg/dL (5.6 mmol/L) to 300 mg/dL (16.7 mmol/L). The SHG classification with the highest number of patients was >150 mg/dL (201,608), followed by >180 mg/dL (198,465), and >200 mg/dL (40,354) (S1 Fig). In several studies, patients were classified into different groups depending on the magnitude of HG.

Clinical practice was also highly variable and very often incompletely reported. The sampling site was capillary, arterial, or venous. The meter used was either a blood gas analyser, a point-of-care glucometer, or a central laboratory interface (S1 Fig). Ten studies used more than one of these meters to assess BG levels.

There was considerable heterogeneity and occasional ambiguity in the reporting of the timing of samples used to assess BG levels. While some studies reported the timescale of samples used (e.g. those taken in the first 24 or 48 h), others reported the frequency at which samples were obtained (e.g. hourly or daily). In many studies, BG was measured both at admission and during ICU stay, with most measurements obtained within the first 72 h after admission (S1 Fig). BG was usually calculated as an average of all measures taken or as the highest value recorded in a given time period. It was only very rarely reported as a time-weighted average [54].

When reported, the target BG ranges were also very heterogeneous (S1 Fig); while six studies reported the use of a treatment protocol for hyperglycaemia [3,44,49,58,61,62], others reported that control of hyperglycaemia was not formalised and at the discretion of the attending critical care physician [46,60]. The most common target range was 80–110 mg/dL, which was used in 4 studies. The ranges used in the remaining studies varied, but most targeted BG levels of <150 mg/dL (S1 Fig).
Patients’ characteristics. Besides demographic data (age, gender), the descriptions of clinical characteristics of the patients were variable, including the type of admission, and severity score (S2 Fig). The majority of studies reported the number of patients with diabetes in their population; however, the subsequent processes were varied, with some studies including a mix of diabetic and non-diabetic patients while others excluded diabetic patients entirely. More studies were conducted in mixed populations of both diabetic and non-diabetic patients than in separate populations (S2 Table).
Study outcomes

Most of the included studies assessed the impact of high BG levels on clinical outcomes as the primary study objective. However, the outcome variables reported varied widely (Fig 2). Although part of the scoping review, ICU-acquired weakness was not reported as an outcome in any of the included studies.

**SHG and mortality.** Mortality was reported in 38 studies across both trauma and mixed ICUs (Fig 2; S2 Fig). Most of the studies reported hospital mortality, or short-term mortality (7-, 14-, 21-, or 30-day mortality), and only one reported ICU mortality (Fig 2). No studies reported data on long-term mortality rates. The ranges of hospital mortality differed widely, ranging between 3.1–43.0% [34,35,40,42,44,45,47,49,53,55,59,66,67]; reported ICU mortality ranged between 1.2–35.6% [3,32,54,60,62,63,69]. The heterogeneity in the types of mortality reported precluded the calculation of a mean mortality rate from the included studies. Of note, there was no report of the observed/expected mortality rate.

S2 Table shows unadjusted mortality levels in hyperglycaemic and non-hyperglycaemic patients in trauma and mixed ICUs. Where reported, ORs ranged between 1.00–17.1. However, mortality varied across all studies in terms of the cut-off point for BG, diabetes status, ICU type, underlying disease, type of insulin control, and mortality measurement time-point.

Mortality levels were stratified by diabetic status in two studies [56,58]; one of them showed that patients with diabetes and mean BG between 110 mg/dL (6.1 mmol/L)–180 mg/dL (10.0 mmol/L) had a lower mortality rate than patients with diabetes and mean BG between 80 mg/dL (4.4 mmol/L)–110 mg/dL (6.1 mmol/L) [56]. Two studies reported mortality levels exclusively in diabetic patients [30,50].

Fourteen studies that assessed the impact of hyperglycaemia on mortality also determined whether hyperglycaemia was an independent risk factor for mortality [3,32,34,37,40,42,47–50,52,54,56,64]. Most of the studies showed that higher BG levels were associated with a higher risk of mortality even after adjusting for confounding variables, where reported ORs ranged between 1.00–17.1.

---

**Table 1. Setting: Study location and ICU type.**

| Setting                   | No. of studies | No. of patients | References |
|---------------------------|----------------|-----------------|------------|
| Study location            |                |                 |            |
| USA and Canada            | 28             | 523,271         | [30,32–58] |
| Europe                    | 6              | 9,560           | [3,39–63]  |
| Middle East               | 3              | 1,152           | [64–66]    |
| Asia                      | 2              | 328             | [67,68]    |
| South America             | 2              | 1,165           | [69,70]    |
| Australia                 | 1              | 1,000           | [71]       |
| ICU type                  |                |                 |            |
| Trauma                    | 17             | 8,383           | [33,34,36–39,41,42,44,45,47,49,53,55,59,66,67] |
| Mixed medical/surgical    | 8              | 255,544         | [3,32,51,54,56,61,62,69] |
| Mixed medical/surgery/cardiac/coronary | 5        | 267,655         | [35,40,50,58,70] |
| Head/brain/neurologic trauma | 5            | 1,822           | [48,60,64,65,68] |
| Medical                   | 2              | 500             | [30,63]    |
| General                   | 2              | 1,170           | [46,71]    |
| Burn and trauma           | 1              | 609             | [43]       |
| Orthopaedic trauma        | 1              | 187             | [57]       |
| Mixed neurologic medical/surgical/trauma | 1        | 606             | [52]       |

https://doi.org/10.1371/journal.pone.0194952.t001

---
Infections in hyperglycaemic and non-hyperglycaemic patients. Twelve publications reported data on infections in ICUs (Fig 2 and S2 Table) from a total of 8,564 patients. The percentages of patients with infections varied from a low 12.5% (BG >150 mg/dL [8.3 mmol/L]) [41] to a high 61% (BG 140–219 mg/dL [7.8–12.2 mmol/L]) [42] (S2 Table). Details on the type of infections were provided in all studies: they included bloodstream, respiratory, genitourinary, and surgical site infections.

Eight studies assessed whether hyperglycaemia was a risk factor for developing infections [34,36–39,42,57,62], and five of these [34,36,38,39,57] identified it as an independent risk factor, where reported, ORs ranged between 0.44–5.02. Across these latter studies, hyperglycaemia as an independent risk factor was expressed as a hyperglycaemic index [57] (ORa = 1.8, 95% CI 1.3–2.5), as BG levels ≥200 mg/dL (11.1 mmol/L) (P = 0.02, no odds ratios reported) [36], (P = 0.007, no odds ratios reported) [38] or >135 mg/dL (7.5 mmol/L) [34] (urinary tract infections; ORa = 3.3, 95% CI 1.21–8.8; pneumonia; ORa = 2.8, 95% CI 0.98–8.0) or as a pattern of glucose control [39].

Hyperglycaemia and length of stay in ICU/hospital. ICU and hospital stays were reported by many studies, although not all studies reported both variables. Length of stay was consistently reported across studies and settings as measures of the central tendency (mean or median), and was usually stratified by BG levels. Among studies that reported ICU length of stay (Fig 2), the mean duration was 10.9 days (range 1.9–34) in patients with SHG; this value includes patients categorised as having moderate or severe SHG. In patients with normal BG
levels, the mean length of ICU stay was 9.1 days (range 1–30 days). It should be noted that some studies excluded patients who stayed in the ICU for less than 24 or 48 h, which may have affected the findings. The role of hyperglycaemia as a predictor of ICU length of stay was investigated in only one trauma ICU study [34].

**Resource use in hyperglycaemic and non-hyperglycaemic patients.** More studies reported time on mechanical ventilation (13 studies; 200,549 patients) (Fig 2) than blood transfusions (three studies; 1,284 patients) or renal replacement therapy (two studies; 194,877 patients). Time on ventilation was longer (range: 1 day [41,45]– 25 days [55]) for patients with hyperglycaemia than for those without, and this difference was found to be significant in five studies [37,39,41,42,61] (S2 Table). Hyperglycaemic patients were administered more units of blood (3.7 units SD = 2.5) than non-hyperglycaemic patients (3.1 units SD = 2.3) on average, but this difference was not statistically significant [38].

Two studies reported data on renal replacement treatment [54,63], revealing a higher number of hyperglycaemic patients undergoing dialysis than non-hyperglycaemic patients (4.2% versus 2.4%) [54] (S2 Table).

None of the included studies assessed whether hyperglycaemia was a risk factor for increased time on mechanical ventilation, an increased number of blood transfusions, or renal replacement therapy.

**Discussion**

This systematic scoping review was performed to identify the characteristics, extent, and results of existing research conducted in observational settings on the association between occurrence of hyperglycaemia in adult patients admitted in ICUs and various outcomes. To the authors’ knowledge, this is the first scoping review to systematically assess the clinical burden of SHG in ICUs in observational studies, as the majority of evidence synthesis data currently available on hyperglycaemia have focused mainly on RCTs, which can differ from the exact conditions of clinical practice [72]. Even though an association between SHG and worsened outcomes was acknowledged by 43% of the studies identified (as reported by 18 of the 42 included studies reporting on either mortality, infections or ICU length of stay), our results revealed great variability in terms of reporting and conduct of the included studies, illustrating a high heterogeneity in clinical practice across settings, patients, and geographies.

Among the sources of heterogeneity, the types of ICUs widely differed, especially considering the lack of standardization in the definitions of trauma, mixed, medical, surgical units. Fewer studies reported data on mixed than on trauma ICU patients, although more patients were admitted in mixed than in trauma ICUs. Few studies provided detailed information on how BG was measured (frequency or time-point of measures, site of blood sampling), or the techniques used to monitor or analyse BG in critically ill patients, in spite of the current recommendation to report these data [73]. No studies conducted on trauma ICU patients reported such evidence, while differences in the accuracy of measurement can be relevant, especially in case of peripheral hypoperfusion, or in the presence of physico-chemical confounding factors [73]. This information is essential to accurately compare and understand the results of the various studies. Regarding outcomes reporting, very few studies had a defined time-point to measure mortality, for example. Additionally, hypoglycaemia was reported in only nine studies [3,30,51,52,54,55,61,63,70], in spite of the current recommendations that it should be reported alongside hyperglycaemia due to its association with increased mortality and morbidity [73]. This lack of important information could reflect a lower focus interest for dysglycemia in ICU patients than in patients with diabetes, in relation with the much higher complexity of the critically ill.
In spite of these broad disparities, the SHG is associated with a significant clinical burden defined a priori as a combination of patients’ severity of disease, including the outcome variables improved during the pioneering study [4] and the use of available resources. Hopefully, the SHG-related clinical burden could be decreased by the appropriate control, prevention, treatment, and monitoring, when specific categories of patients and situations could be identified. Unfortunately, the current evidence is probably too heterogeneous to allow such identification. In fact, the results of this study are comparable to those reported in 2008 by Eslami et al. [74] in a systematic review on quality indicators for tight glycaemic control in critically ill patients. The same review also identified high variability and ambiguity in the definitions and threshold values for reporting hyperglycaemia, noting the reduced comparability among studies for these reasons [74]. In line with other systematic reviews [13,25,75,76], our review has also pointed out that the heterogeneous nature of the methods used in studies in this field prevents meta-analysis of data, making narrative summaries more appropriate. However, narrative summaries are not as informative as meta-analyses for clinical decision-making processes as they do not allow the calculation of pooled effect estimates [77]. Moreover, the issue of whether HG should be considered as a marker of the severity of disease or as a potentially modifiable risk factor cannot be solved with the current set of available data.

Future studies should focus more on providing details on BG sampling techniques, BG measurement protocols, and on clearly defining outcomes, including their time-points of measurement. Furthermore, studies should more frequently report on the potential differences in the clinical burden of SHG between diabetic and non-diabetic patients. Indeed, the optimal BG value could differ between diabetic or chronically hyperglycaemic patients [78].

Other unexplored outcomes of clinical burden, such as ICU-acquired weakness or nursing workload, the amount of transfusion should also become the focus of future observational studies. Of particular interest is ICU-acquired weakness as its impact goes beyond the hospitalisation phase; it specifically contributes to the physical limitations in ICU survivors that are associated with reduced health-related quality of life and higher one-year mortality [79].

Our scoping review has several limitations. First, our searches were limited to studies published in English, potentially leading to language bias and exclusion of relevant articles published in other languages. Second, ICU-acquired weakness was defined according to the most recent terminology, excluding terms such as polyneuromyopathy, critical illness myopathy, or polyneuropathy. This was done at both the screening and data-extraction stage, which may explain why no studies were found to report data on ICU-acquired weakness. Finally, scoping reviews are not intended to assess the quality of the literature analysed. Thus, the conclusions of this review are based on the existence of studies rather their intrinsic quality. Nevertheless, this scoping review provides a comprehensive overview of the existing research on hyperglycaemia in ICUs in observational settings, by reporting data collected from more than 500,000 critically ill patients, which is one of the highest numbers of patients ever studied in intensive care medicine.

Conclusions

The clinical consequences of SHG represent adverse outcomes for acutely ill patients. The understanding of the magnitude of this burden is limited due to the great variability observed in studies’ reporting and conduct. This highlights an urgent need for a consensus and unified criteria for measuring and controlling SHG, if better care is to be provided. Recommendations have been previously published by clinical experts in the acute care field [80], making these recommendations clinically meaningful. These recommendations include standardisation of blood glucose sampling, as well as the metrics to report glycaemic control. Such recommendations were published with the aim to improve glycaemic control in daily clinical practice, while also minimising the disparities
facilitating the interpretation and comparison of clinical trials. Individualised thresholds for different patient subgroups might be the way forward in the management of SHG, but this approach will only become the standard in clinical practice if an improvement in patient outcomes is supported by a consistent and homogeneously conducted and reported body of evidence.

**Supporting information**

**S1 Fig. Blood glucose (BG) variables by number of studies and patients.** A. Stress hyperglycaemia (SHG) definition. B. BG sampling site. C. Meter used for BG sampling. POC/gluc, point-of-care/glucosemeter; BGA, blood gas analyser; Lab, laboratory D. Timing of BG sampling. E. Target BG range. NR, not reported.

*Data from the study by Falciglia et al. (2009) were not included in this graph, as the study compiled findings from 173 hospitals with more than 250,000 patients. As it also considered multiple HG definition categories (all >111 mg/dL), inclusion of this study would have skewed the findings. (PPTX)*

**S2 Fig. Patient characteristics by number of studies and patients.** A. Acute Physiology and Chronic Health Evaluation (APACHE) score. B. Mortality type. ICU, intensive care unit; NR, not reported.

**(PPTX)**

**S1 Table. Search strategy for Medline and Medline In-Process.**

**(DOCX)**

**S2 Table. Mortality, infections, length of stay, and resource use in patients with or without hyperglycaemia in trauma and mixed ICUs.** aRespiratory, genito-urinary, bloodstream; brespiratory infections; cgenitourinary tract infections; dblood infections; eintra-abdominal infections; skin/soft tissue infections; grespiratory infections, genito-urinary tract infections, wound or skin infections; hpneumonia, urinary tract infections, bacteraemia, intra-abdominal abscess, wound infection, open fracture infection; i(pneumonia, line sepsis, bacteraemia, wound infection, abscess; joverall ICU mortality; kweek 1 mortality; lwk 2 mortality; mmweek 3 mortality; nbacteraemia; urinary tract infections; npneumonia in the third week; ssurgical site infections; tspneumonia, urinary tract infection, bloodstream infection, surgical site infection, intra-abdominal abscess, Clostridium difficile colitis, meningitis, and sinusitis; tskin/ wound infections; uother infections; vpneumonia; wound infections.

BG, blood glucose; CI, confidence interval; CIT, continuous intravenous regular human insulin infusion; HG, hyperglycaemia; HGI, hyperglycaemic index; HR, hazard ratio; ICU = intensive care unit; IIT, intensive insulin control; IQR = interquartile range; ISS = injury severity score; max, maximum; NA = not applicable; NPH = neutral protamine Hagedorn; NR, not reported; OR, odds ratio; ORa, odds ratio adjusted; PH, persistent hyperglycaemia; RR, risk ratio; RRa, risk ratio adjusted; SD, standard deviation; SE, standard error; SEM, standard error of the mean; SIT, supplemental intermittent intravenous regular human insulin therapy; TBI, traumatic brain injury; TIR-hi, time in targeted blood glucose range above the median value; TIR-lo, time in targeted blood glucose range below the median value. *P<0.05; **P<0.01; †Nosocomial infections.

**(DOC)**

**Acknowledgments**

We would like to thank Fiona Weston for editing the manuscript and Dave Fox for developing the search strategy.
Author Contributions

Conceptualization: Aurélie Danel, Montserrat Miret, Jean-Charles Preiser.

Data curation: Nicholas Pooley.

Formal analysis: Elena Olariu, Nicholas Pooley, Aurélie Danel, Montserrat Miret, Jean-Charles Preiser.

Funding acquisition: Aurélie Danel, Montserrat Miret.

Investigation: Elena Olariu, Nicholas Pooley.

Methodology: Elena Olariu, Nicholas Pooley.

Project administration: Elena Olariu.

Resources: Elena Olariu.

Writing – original draft: Elena Olariu.

Writing – review & editing: Elena Olariu, Nicholas Pooley, Aurélie Danel, Montserrat Miret, Jean-Charles Preiser.

References

1. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Crit Care. 2013; 17: 305. https://doi.org/10.1186/cc12514 PMID: 23470218
2. Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. Lancet. 2009; 373: 1798–1807. https://doi.org/10.1016/S0140-6736(09)60553-5 PMID: 19465235
3. Siegelaar SE, Hermans J, Oudemans-van Straaten HM, van der Voort PHJ, Zandstra DF, et al. Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. Crit Care. 2010; 14: R224. https://doi.org/10.1186/cc9369 PMID: 21143980
4. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensiv e insulin therapy in critically ill patients. N Engl J Med. 2001; 345: 1359–67. https://doi.org/10.1056/NEJMoa011300 PMID: 11794168
5. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med. 1982; 72: 439–50. PMID: 7036735
6. Corstjens AM, van der Horst ICC, Zijlstra JG, Groeneveld ABJ, Zijlstra F, Tulleken JE, et al. Hyperglycaemia in critically ill patients: marker or mediator of mortality? Crit Care. 2006; 10: 216. https://doi.org/10.1186/cc4957 PMID: 16834760
7. Kadri Z, Danchin N, Vaur L, Cottin Y, Guéret P, Zeller M, et al. Major impact of admission glycaemia on 30 day and one year mortality in non-diabetic patients admitted for myocardial infarction: results from the nationwide French USIC 2000 study. Heart. 2006; 92: 910–5. https://doi.org/10.1136/hrt.2005.073791 PMID: 16339808
8. Deckers JW, van Domburg RT, Akkerhuis M, Nauta ST. Relation of Admission Glucose Levels, Short- and Long-Term (20-Year) Mortality After Acute Myocardial Infarction. Am J Cardiol. 2013; 112: 1306–1310. https://doi.org/10.1016/j.amjcard.2013.06.007 PMID: 23866731
9. Krinsley JS, Preiser J-C, 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: 318–330. https://doi.org/10.4158/EP161532.OR PMID: 27967228
10. Gray CS, Scott JF, French JM, Alberti KGMM, O’Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. Age Ageing. 2004; 33: 71–7. PMID: 14695867
11. Gornik I, Vujaklija-Brajkovic A, Renar IP, Gasparovic V. A prospective observational study of the relationship of critical illness associated hyperglycaemia in medical ICU patients and subsequent development of type 2 diabetes. Crit Care. 2010; 14: R130. https://doi.org/10.1186/cc9101 PMID: 20615210
12. McAllister DA, Hughes KA, Lone N, Mills NL, Sattar N, McKnigbt J, et al. Stress hyperglycaemia in hospitalised patients and their 3-year risk of diabetes: a Scottish retrospective cohort study. Bell D, editor. PLoS Med. 2014; 11: e1001708. https://doi.org/10.1371/journal.pmed.1001708 PMID: 25136809
13. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016; 20: 301. https://doi.org/10.1186/s13054-016-1471-6 PMID: 27677709

14. Preiser J-C, de Longueville C. Could type 2 diabetes be a component of the post-intensive care syndrome? Crit Care. 2017; 21: 26. https://doi.org/10.1186/s13054-017-1607-3 PMID: 28173874

15. De La Rosa GD, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, et al. Strict glycemic control in patients hospitalized in a mixed medical and surgical intensive care unit: a randomized clinical trial. Crit Care. 2008; 12: R120. https://doi.org/10.1186/cc77017 PMID: 18799004

16. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. N Engl J Med. 2008; 358: 125–139. https://doi.org/10.1056/NEJMoa0810625 PMID: 18184958

17. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY-S, Blair D, Foster D, et al. Intensive versus Conventional Glucose Control in Critically Ill Patients. N Engl J Med. 2009; 360: 1283–1297. https://doi.org/10.1056/NEJMoa0810625 PMID: 19318384

18. Preiser J-C, 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; 35: 1738–1748. https://doi.org/10.1007/s00134-009-1585-2 PMID: 19636533

19. COIITSS Study Investigators, Annane D, Cariou A, Maxime V, Azoulay E, D’honore G, et al. Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults. JAMA. 2010; 303: 341. https://doi.org/10.1001/jama.2010.2 PMID: 20103758

20. Kalfon P, Giradreau B, Ichai C, Guerrini A, Brechot N, Cinotti R, et al. Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial. Intensive Care Med. 2014; 40: 171–181. https://doi.org/10.1007/s00134-013-3189-0 PMID: 24420499

21. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemiri AA, Memish ZA, Haddad SH, et al. Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients*. Crit Care Med. 2008; 36: 3190–3197. https://doi.org/10.1097/CCM.0b013e3181f8f1aa PMID: 18936702

22. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY-S, Blair D, Foster D, et al. Intensive versus Conventional Glucose Control in Critically Ill Patients. N Engl J Med. 2009; 360: 1283–1297. https://doi.org/10.1056/NEJMoa0810625 PMID: 19318384

23. Preiser J-C, 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; 35: 1738–1748. https://doi.org/10.1007/s00134-009-1585-2 PMID: 19636533

24. Kuppingner D, Hartl WH. In search of the perfect glucose concentration for hospitalized patients: a brief review of the meta-analyses. Nutrition. 2013; 29: 708–12. https://doi.org/10.1016/j.nut.2012.11.019 PMID: 23422535

25. Manik PE, Preiser J-C. Toward understanding tight glycemic control in the ICU: a systematic review and meta-analysis. Chest. 2010; 137: 534–51. https://doi.org/10.1378/chest.09-1737 PMID: 20018803

26. Mesotten D, Preiser J-C, Kosiborod M. Glucose management in critically ill adults and children. Lancet Diabetes Endocrinol. 2015; 3: 723–733. https://doi.org/10.1016/S2213-8587(15)00223-5 PMID: 26071884

27. Arsey H, O’Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. Taylor and Francis Group Ltd; 2005; 8: 19–32. https://doi.org/10.1080/1364557032000119616

28. Levac D, Colquhoun H, O’Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010; 5: 69. https://doi.org/10.1186/1748-5908-5-69 PMID: 20854677

29. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015; 13: 141–146. https://doi.org/10.1097/XEB.0000000000000050 PMID: 26134548

30. Schlusel AT, Holt DB, Crawley EA, Lustik MB, Wade CE, Ueyhara CF. Effect of diabetes mellitus on outcomes of hyperglycaemia in a mixed medical surgical intensive care unit. J Diabetes Sci Technol. 2011; 5: 731–40. https://doi.org/10.1177/1932296811005000328 PMID: 21722589

31. Schlusel AT, Holt DB, Crawley EA, Lustik MB, Wade CE, Ueyhara CFT. Effects of Hyperglycaemia and Continuous Intravenous Insulin on Outcomes of Surgical Patients. J Surg Res. 2012; 176: 202–209. https://doi.org/10.1016/j.jss.2011.07.004 PMID: 21920548

32. Umpeirzez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycaemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes. J Clin Endocrinol Metab. 2002; 87: 978–982. https://doi.org/10.1210/jcem.87.3.8341 PMID: 11889147
33. Jeremitsky E, Omer L, Dunham CM, Protetch J, Rodriguez A. Harbingers of Poor Outcome the Day after Severe Brain Injury: Hypothermia, Hypoxia, and Hypoperfusion. J Trauma Inj Infect Crit Care. 2003; 54: 312–319. https://doi.org/10.1097/01.TA.000037876.37236.D6 PMID: 12579057

34. Yendamuri S, Fulda GJ, Tinkoff GH. Admission Hyperglycemia as a Prognostic Indicator in Trauma. J Trauma Inj Infect Crit Care. 2003; 55: 33–38. https://doi.org/10.1097/01.TA.0000074434.39928.72 PMID: 12855878

35. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003; 78: 1471–8. https://doi.org/10.4065/78.12.1471 PMID: 14661676

36. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Association between hyperglycemia and increased mortality in a heterogeneous population of critically ill patients. Crit Care Med. 2005; 33: 2772–7. PMID: 16352959

37. Bochicchio G V, Salzano L, Joshi M, Bochicchio K, Scalea TM. Admission hyperglycemia is predictive of morbidity and mortality in trauma patients who require immediate operative intervention. Am Surg. 2005; 71: 171–4. PMID: 16022019

38. Bochicchio G V, Sung J, Joshi M, Bochicchio K, Johnson SB, Meyer W, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma. 2005; 58: 921–4. PMID: 15920404

40. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann M-C, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med. 2005; 33: 1353–8. https://doi.org/10.1097/01.CCM.0000168367.26205.95 PMID: 16486427

41. Duane TM, Dechert T, Dalesio N, Wolfe LG, Aboutanos MB, Malhotra AK, et al. Is blood sugar the next lactate? Am Surg. 2006; 72: 613-7-8.

42. Bochicchio G V, Joshi M, Bochicchio KM, Pyle A, Johnson SB, Meyer W, et al. Early hyperglycemic control is important in critically injured trauma patients. J Trauma. 2007; 63: 1353–8. https://doi.org/10.1097/TA.0b013e318190068f PMID: 17879682

43. Shin S, Brits RC, Reed SF, Collins J, Weireter LJ, Brits LD. Early glucose normalization does not improve outcome in the critically ill trauma population. Am Surg. 2007; 73: 769–72; discussion 772. PMID: 17879682

44. Gale SC, Sicoutris C, Reilly PM, Schwab CW, Gracias VH. Poor glycemic control is associated with increased mortality in critically ill trauma patients. Am Surg. 2007; 73: 454–60. PMID: 17520998

45. Shin S, Brits RC, Reed SF, Collins J, Weireter LJ, Brits LD. Early glucose normalization does not improve outcome in the critically ill trauma population. Am Surg. 2007; 73: 769–72; discussion 772. PMID: 17879682

46. Duane TM, Dechert T, Dalesio N, Wolfe LG, Aboutanos MB, Malhotra AK, et al. Is blood sugar the next lactate? Am Surg. 2006; 72: 613-7-8.

47. Smith RS, Fry WR, Philip FH, Philip AS, Berry SD, Helmer S. Mild hyperglycemia, but not glucagon-like peptide 1 predicts poor outcome after injury. Am J Surg. 2012; 204: 915–920. https://doi.org/10.1016/j.amjsurg.2012.05.016 PMID: 23231933
54. 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. https://doi.org/10.1097/CCM.0b013e3182656a65 PMID: 22971590

55. Dickerson RN, Wilson VC, Maish GO, Croce MA, Minard G, Brown RO. Transitional NPH Insulin Therapy for Critically Ill Patients Receiving Continuous Enteral Nutrition and Intravenous Regular Human Insulin. J Parenter Enter Nutr. 2013; 37: 506–516. https://doi.org/10.1177/0148607112458526 PMID: 22914894

56. Krinsley JS, Eg 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; 17: R37. https://doi.org/10.1186/cc12547 PMID: 23452622

57. Richards JE, Kauffmann RM, Obremskey WT, May AK. Stress-induced hyperglycemia as a risk factor for surgical-site infection in non-diabetic orthopedic trauma patients admitted to the intensive care unit. J Orthop Trauma. 2013; 27: 16–21. https://doi.org/10.1097/BOT.0b013e31825d60e5 PMID: 22588532

58. Krinsley JS, Preiser J-C. Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults. Crit Care. 2015; 19: 179. https://doi.org/10.1186/s13054-015-0908-7 PMID: 25927986

59. Kreutziger J, Rafetseder A, Mathis S, Wenzel V, El Attal R, Schmid S. Admission blood glucose predicted haemorrhagic shock in multiple trauma patients. Injury. 2015; 46: 15–20. https://doi.org/10.1016/j.injury.2014.09.018 PMID: 25441172

60. Meier R, Béchir M, Ludwig S, Sommerfeld J, Keel M, Steiger P, et al. Differential temporal profile of lower 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. https://doi.org/10.1186/cc6974 PMID: 18680584

61. Van Ackerbroeck S, Schepens T, Janssens K, Jorens PG, Verbrugghe W, Collet S, et al. Incidence and predisposing factors for the development of disturbed glucose metabolism and Diabetes mellitus APer Intensive Care admission: the DIAFIC study. Crit Care. 2015; 19: 355. https://doi.org/10.1186/s13054-015-1064-9 PMID: 26428846

62. Donati A, Damiani E, Domizi R, Botticelli L, Castagnani R, Gabbanelli V, et al. Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. Crit Care Resusc. 2014; 16: 13–23. PMID: 24588431

63. Lacherade J-C, Jabre P, Bastuji-Garin S, Grimaldi D, Fangio P, Théron V, et al. Failure to achieve glycemic control despite intensive insulin therapy in a medical ICU: incidence and influence on ICU mortality. Intensive Care Med. 2007; 33: 814–21. https://doi.org/10.1007/s00134-007-0543-0 PMID: 17431584

64. Bahilou M, Chelly H, Ben Hamida M, Ben Hamida C, Ksibi H, Kallel H, et al. Prognosis of traumatic head injury in South Tunisia: a multivariate analysis of 437 cases. J Trauma. 2004; 57: 255–61. PMID: 15345970

65. Chabok SY, Dafchahi MA, Mohammadi H, Shabbidar S. Admission hyperglycemia in head injured patients. Acta Medica Iranica. Univ; 2009.

66. Safavi M, Honarmand A. The impact of admission hyperglycemia or hypoalbuminemia on need ventilator, time ventilated, mortality, and morbidity in critically ill trauma patients. Ulus Travma Acil Cerrahi Derg. 2009; 15: 120–9. PMID: 19353310

67. Lionel K, John J, Sen N. Glycated hemoglobin A: A predictor of outcome in trauma admissions to intensive care unit. Indian J Crit Care Med. 2014; 18: 21. https://doi.org/10.4103/0972-5229.125431 PMID: 24550609

68. Santhanam R, Pillai S V, Kolluri SVR, Rao UM. Intensive care management of head injury patients without routine intracranial pressure monitoring. Neurol India. 2007; 55: 349–54. PMID: 18040107

69. Lucas MCS, Fayh APT. Nutritional status, hyperglycemia, early nutrition, and mortality of patients hospitalized in an intensive care unit. Rev Bras Ter intensiva. 2012; 14: 157–61. PMID: 23917763

70. Leite SA, Locatelli SB, Niece SP, Oliveira AR, Tockus D, Tosin T. Impact of hyperglycemia on morbidity and mortality, length of hospitalization and rates of re-hospitalization in a general hospital setting in Brazil. Diabetol Metab Syndr. 2010; 2: 49. https://doi.org/10.1186/1758-5966-2-49 PMID: 20663317

71. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundrarajan K, Reddi BAJ, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014; 40: 973–80. https://doi.org/10.1007/s00134-014-3287-7 PMID: 24760120

72. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015; 16: 495. https://doi.org/10.1186/s13063-015-1023-4 PMID: 26530985
73. Finfer S, Wernerman J, Preiser J-C, Cass T, Desaive T, Hovorka R, et al. Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013; 17: 229. https://doi.org/10.1186/cc12537 PMID: 23767816

74. Eslami S, de Keizer NF, de Jonge E, Schultz MJ, Abu-Hanna A. A systematic review on quality indicators for tight glycaemic control in critically ill patients: need for an unambiguous indicator reference subset. Crit Care. 2008; 12: R139. https://doi.org/10.1186/cc7114 PMID: 19014427

75. Merrill A, Jones S. Effectiveness of tight glycemic control in the medical Intensive Care Unit: a systematic review. JBI Libr Syst Rev. 2011; 9: 418–436. PMID: 27820532

76. Eslami S, Taherzadeh Z, Schultz MJ, Abu-Hanna A. Glucose variability measures and their effect on mortality: a systematic review. Intensive Care Med. 2011; 37: 583–93. https://doi.org/10.1007/s00134-010-2129-5 PMID: 21279326

77. Yuan Y, Hunt RH. Systematic Reviews: The Good, the Bad, and the Ugly. Am J Gastroenterol. 2009; 104: 1086–1092. https://doi.org/10.1038/ajg.2009.118 PMID: 19417748

78. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care. American Diabetes Association; 2008; 31: 1473–8. https://doi.org/10.2337/dc08-0545 PMID: 18540046

79. Hermans G, Van den Bergh G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015; 19: 274. https://doi.org/10.1186/s13054-015-0993-7 PMID: 26242743

80. Finfer S, Wernerman J, Preiser J-C, Cass T, Desaive T, Hovorka R, et al. Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013; 17: 229. https://doi.org/10.1186/cc12537 PMID: 23767816