Review article

Update on glucose in critical care

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ABSTRACT

The aim of this review is to summarize recent developments on the mechanisms involved in stress hyperglycemia associated with critical illness. Different aspects of the consequences of stress hyperglycemia as well as the therapeutic approaches tested so far are discussed: the physiological regulations of blood glucose, the mechanisms underlying stress hyperglycemia, the clinical associations, and the results of the prospective trials and meta-analyses to be taken into consideration when interpreting the available data. Current recommendations, challenges, and technological hopes for the future are be discussed.

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Introduction

The interest in metabolic changes associated with critical illness, and in particular the issue of stress hyperglycemia (SH) has increased greatly over the past 20 y. SH generally refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes [1,2]. According to the American Diabetes Association (ADA) [3], there are two categories of SH depending on preexistence of diabetes:

- Fasting glucose >125 mg/dL or a record >200 mg/dL at any point in its evolution without evidence of previous diabetes;
- Pre-existing diabetes with deterioration of pre-illness glycemic control.

The most relevant threshold for SH in patients with preexisting diabetes probably varies according to the chronic blood glucose (BG) level. Likewise, the magnitude of SH likely varies over time, as the typical stress response includes successive phases [4,5]. Basically, the metabolic response to stress is stereotypical, regardless of the initial trigger [4], aiming at a reorganization of delivery of

energy substrates by promoting organs whose functioning is essential to the survival of the patient undergoing aggression [6].

Mechanisms of stress hyperglycemia

SH results from changes of the hormonal and neural signals involved in the regulation of the metabolism of carbohydrates, usually known as insulin resistance (IR), that is, "the inability of insulin to adequately stimulate glucose uptake into skeletal muscle or to inhibit gluconeogenesis in the liver" [6]. The translocation of glucose transporters (GLUT) is the prominent mechanism for the modulation of glucose transport across the cell membranes [7]. The modulation of glucose fluxes across cell membranes by the translocation of transporters is designed to supply sufficient amounts of glucose to the non−insulin-mediated glucose uptake (NIMGU) tissues. This mechanism is usually considered adaptive as the provision of glucose to these NIMGU tissues, including immune cells, brain, and kidney, is indeed needed to survive the injury. GLUT-1 is the predominant transporter for NIMGU, and GLUT-2 regulates the flow of glucose across liver and gut cell membranes. In contrast, after injury the insulin-mediated glucose uptake, mainly adipose tissue and skeletal muscles, are less avid for glucose, as reflected by the downregulation of the GLUT-4 receptors.

The pathophysiology behind SH is very different from the chronic hyperglycemia of patients with type 2 diabetes. The etiology of type 2 diabetes is a combination of IR and an insufficient secretion of insulin to overcome the resistance, resulting from a

secretory deficit of β cells of the islets of Langerhans. During critical illness, the abrupt development of SH involves complex interactions between some counterregulatory hormones (glucagon, catecholamines, growth hormone, or cortisol), adipokines, and inflammatory cytokines causing both excessive and non-inhibitable production of glucose by the liver and IR of the IMGU tissues [8]. The magnitude of IR is also related to the severity of the condition. Furthermore, hyperglycemia exacerbates the cytokine, inflammatory, and oxidative stress response, potentially setting up a vicious cycle whereby hyperglycemia leads to further hyperglycemia [2,8]. Conversely, resolution of hyperglycemia is associated with normalization of the inflammatory response [9]. IR varies over time and also may be affected by specific treatments during intensive care unit (ICU) stay. For example, insulin sensitivity is much lower and more variable during therapeutic hypothermia, which often is used during 24 h to treat cardiac arrest patients, and consistently increases over time thereafter [10].

The stress-related increase in hepatic output of glucose reflects the intense glycogenolysis and gluconeogenesis. Glycogenolysis is primarily triggered by catecholamines and perpetuated under the influence of epinephrine and cortisol. Gluconeogenesis is stimulated to a larger extent by glucagon than by epinephrine and cortisol. Among the numerous inflammatory mediators released in the acutely ill, tumor necrosis factor-α might promote gluconeogenesis by stimulating glucagon production. For these reasons, in the absence of severe malnutrition the amount of glucose produced by the liver and other gluconeogenic organs during the 3 to 5 d after injury reaches 300 to 400 g/d. Moreover, it is also important to note that an exogenous carbohydrate supply inhibits gluconeogenesis only partially, in contrast to the physiological situation.

IR ultimately promotes a catabolic state implying lipolysis. Elevated circulating free fatty acids in turn exacerbate IR by disrupting end-organ insulin signaling [11] and glycogen synthase [12].

Association between the three domains of dysglycemia and outcome

Before 2001, many studies reported that hyperglycemia is an independent prognostic marker in acutely ill patients [2]. For example, after cardiac surgery glycemia >180 mg/dL, implying poor glucose control,

was consistently and independently associated with an increased rate of postoperative infections and mortality [13]. Survival of a large heterogeneous population of critically ill patients analyzed retrospectively was found to be improved when BG was <150 mg/dL [14].

In 2001, a landmark prospective study [15] reported an impressive benefit of tight glycemic control (TGC; 80–110 mg/dL) and is still fueling many controversies and discussions as several other studies have failed to demonstrate any mortality benefit from TGC versus conventional glycemic control and even associating TGC with a greater risk for hypoglycemia (BG <40 mg/dL) [16–18]. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation trial [16] and subsequent trials [17,19–22] fueled the controversy over the optimal target for glycemic control, resulting in a compromise in favor of an intermediate glycemic target.

Hyperglycemia

From large epidemiologic studies, BG concentrations are raised in severely ill patients, in different settings including emergency departments [23,24], ICUs [14,25,26], and cardiac care units [27]. Observational studies have documented that hyperglycemia after cardiothoracic surgical procedures is associated with twofold increases of the incidence of wound infection [28,29]. Consistently and regardless of the categories of BG concentrations used in the studies, mortality risk rises when BG is >145 mg/dL (Fig. 1). No clear cutoff value of BG concentrations can be defined above which the mortality risk disproportionally or steeply increases. Mortality risk gradually increases in the wide range of severe hyperglycemia (from 145 to 245 mg/dL). This association is substantially blunted in patients with established diabetes [30]. The decreased toxicity of chronic hyperglycemia in patients with diabetes could be explained by intracellular protective mechanisms, such as end-glycation products [31]. This mechanism cannot occur in non-diabetic critically ill patients [32,33].

Hypoglycemia

The definition of severe hypoglycemia used in patients with diabetes cannot be applied directly to those in the ICU who may be
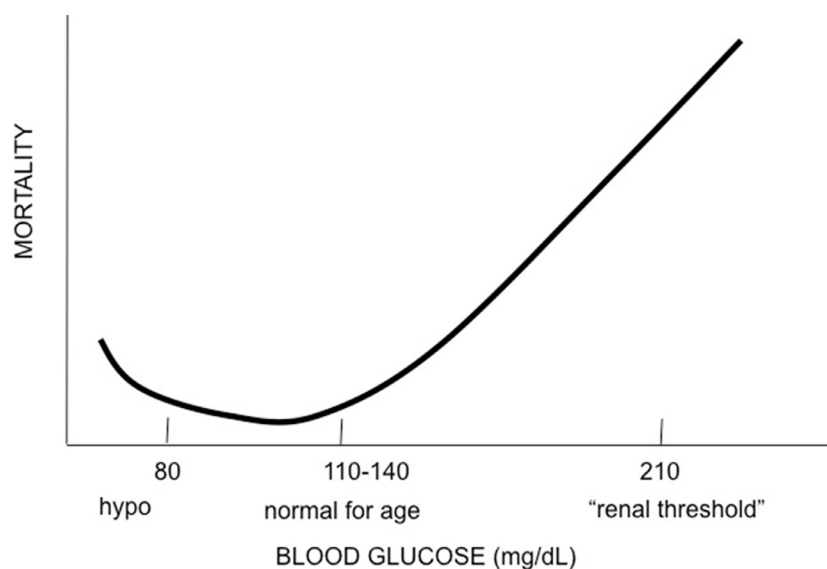

Fig. 1. J-shaped mortality relationship for glycemia for patients in the intensive care unit.

unable to describe clinical signs because of spontaneous or sedation-induced consciousness disorders. Thus, it is arbitrarily and exclusively defined on the basis of an arbitrary BG value.

Hypoglycemia represents the major concern when starting intensive insulin therapy (IIT) and is the major cause of an increased medical and nurse workload. In critically ill adults, the mortality risk associated with hypoglycemia increases linearly with progressive increases in severity of hypoglycemia, regardless of its cause (iatrogenic or spontaneous) [34]. If BG concentrations fall to <70 mg/dL the mortality risk noticeably increases. This cutoff is in line with the most commonly used threshold to define hypoglycemia in patients with diabetes [35]. Severe hypoglycemia in ICU patients was arbitrarily defined in most studies of BG control as BG falling to <40 mg/dL on at least one occasion. Physiologically, long-lasting hypoglycemia will result in decreased glucose availability for tissues in which the uptake of glucose is concentration dependent [36]. The most typical example is the injured brain: Using cerebral microdialysis, Oddo et al. demonstrated that TGC was associated with a greater risk for brain energy crisis and death [37]. These data suggest that TGC may result in hypoglycemia and neuroglycopenia at a time of increased cerebral metabolic demand.

More recently, the concept of relative hypoglycemia has emerged to illustrate the relationship between the control of premorbid glycemia and dysglycemia in ICU [38]. In patients with diabetes, the authors used admission hemoglobin A1c to estimate premorbid baseline BG concentration and defined relative hypoglycemia when glycemic distance (the difference between BG concentrations in ICU and baseline BG concentration) is >30%.

Glycemic variability

Fluctuations of BG, usually described as BG variability, are associated with an increased mortality risk. Notably, inappropriate treatment of hypoglycemia with overdosing of the dextrose bolus can lead to rebound hyperglycemia and increased BG variability (Fig. 2). In a meta-analysis [39], the presence of high BG variability was shown to be an independent risk factor for mortality during critical illness, even after accounting for mean concentrations of BG. However, glycemic variability is the least validated measure because it has been studied less than other measures of glycemia (i.e., hyper- and hypoglycemia) and is highly affected by the frequency of BG measurements and the measure of variability used [40,41]. *Glycemic variability*, defined as the standard deviation of BG, was an independent biomarker of mortality in a large retrospective cohort (N = 7049) [42]. Since then, several observational studies have confirmed the existence of an association between glycemic variability and mortality [43,44]. As glycemic variability is more difficult to define than hypo- or hyperglycemia, a relative high value of the coefficient of variation of >20% has been suggested to define high glycemic variability because it is associated with worse outcomes than values <20%. Therefore, analysis of dysglycemia in critically ill patients should include markers of three domains: hyperglycemia, hypoglycemia, and glycemic variability [45,46].

Intensive insulin therapy

Insulin therapy to lower of BG <180 mg/dL was first assessed in patients after acute myocardial infarction (DIGAMI [Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction]-1 trial; N = 620) [47]. No significant difference in all-cause mortality at 3 mo was recorded between the experimental group and usual care. However, subsequent analyses of mortality at both 1 and 3.5 y of follow-up showed clinically and statistically significant reductions
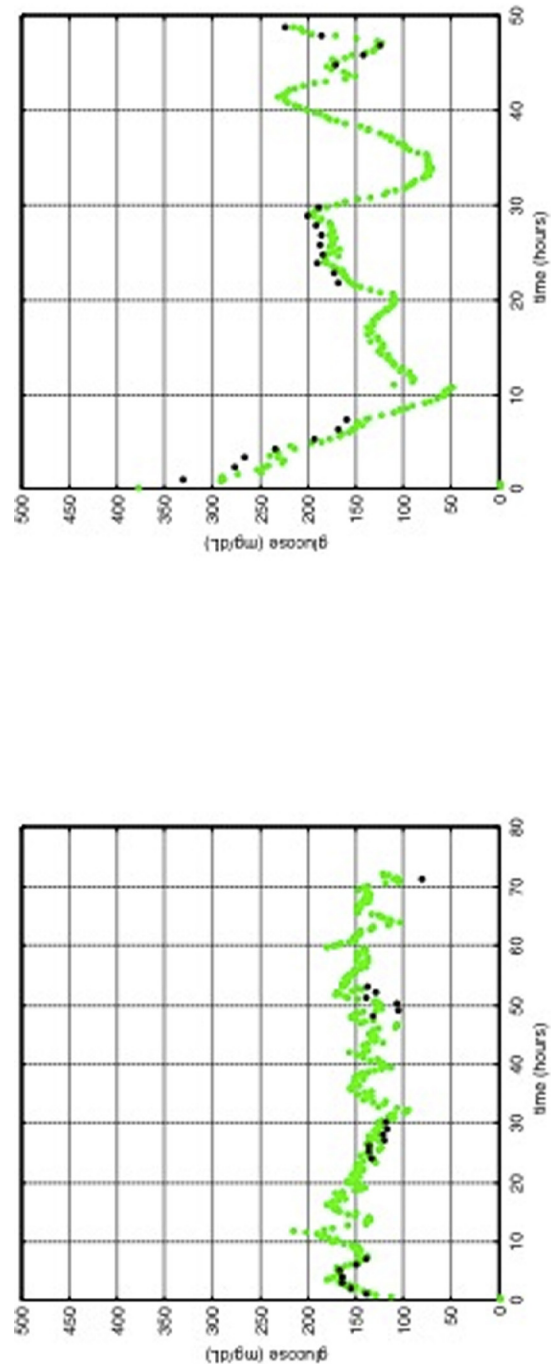

Fig. 2. Individual data from intensive care patients with different glycemic variability. Patient 1 exhibits low glycemic variability (*left panel*); patient 2 exhibits high glycemic variability (*right panel*). Blood glucose data are obtained from continuous monitoring (*green dots*) and intermittent monitoring (*black dots*).

Table 1
Overview of the main adult studies on blood glucose management in the intensive care unit

Study	Study population	Intervention (BG target)	Control (BG target)	Primary outcome variable	Mortality (%)	Incidence of hypoglycemia (%)
Single-center studies						
Van den Berghe et al. (Leuven I), 2001	Surgical (N = 1548)	80–110 mg/dL	180–200 mg/dL	ICU mortality	4.6 vs 8 (P = 0.04)	5 vs 0.7 (P-value not reported)
Van den Berghe et al. (Leuven II), 2006	Medical (N = 1200)	80–110 mg/dL	180–200 mg/dL	ICU mortality	24.2 vs 26.8 (P = NS)	18.7 vs 3.1 (P = 0.001)
Arabi, 2008	Medical-surgical (N = 523)	80–110 mg/dL	180–200 mg/dL	ICU mortality	13,5 vs 17.1 (P = NS)	28,6 vs 3.1 (P = 0.0001)
De La Rosa, 2008	Medical-surgical (N = 523)	80–110 mg/dL	180–200 mg/dL	28-d mortality	36.6 vs 32.4 (P = NS)	8.3 vs 0.8 (P = 0.001)
Multicenter studies						
Brunkhorst et al., 2008 (VISEP)	Sepsis (N= 488)	80–110 mg/dL	180–200 mg/dL	28-d mortality and SOFA	24.7 vs 26 (P = NS)	17.0 vs 4.1 (P = 0.001)
Finfer et al., 2009 (NICE-SUGAR)	Medical-surgical (N = 6104)	80–110 mg/dL	<180 mg/dL	90-d mortality	27.5 vs 24.9 (P = 0.02)	6.8 vs 0.5 (P = 0.001)
Preiser et al., 2009 (GluControl)	Medical (N = 1078)	80–110 mg/dL	140–180 mg/dL	ICU mortality	17.2 vs 15.3 (P = NS)	8.7 vs 2.7 (P = 0.0001)
Kalfon et al., 2014	Medical-surgical (n = 2684)	80–110 mg/dL	<180 mg/dL	90-d mortality	32.3 vs 34.1 (P = NS)	13.2 vs 6.2 (P = 0.01)

BG, blood glucose; ICE, intensive care unit; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation; NS, non-significant; VISEP, Volume Substitution and Insulin Therapy in Severe Sepsis

in all-cause mortality in the experimental group. This survival benefit could not be reproduced in the larger DIGAMI-2 [48] or Hyperglycemia: Intensive Insulin Infusion in Infarction-5 [49] trials. The Randomized Trial to Evaluate the Clinical Value of Intensive Glucose Monitoring and Regulation in Myocardial Infarction-2 study [50], the latest investigation of glucose control in patients with acute myocardial infarction, failed to show a benefit of insulin treatment on the infarct size.

In 2001, after the publication of a study by Van den Berghe [15], TGC was rapidly recommended by the Institute for Health Care Improvement and other national organizations in the United States. However, the results of later randomized controlled trials (RCTs) have dampened the enthusiasm generated by these early results [16,17,19–22,51]. Five years later, Van den Berghe et al. reported findings from their medical ICU [51]. Although failing to reproduce the improvement in survival in the entire set of patients, this study demonstrated a reduction in morbidity in the patients randomized to the TGC group, with a reduction in mortality in the subset of patients requiring critical care for ≥3 d. Two other single-center studies found no decrease in mortality and morbidity in medical and surgical ICU patients receiving IIT [21,22].

Because all the Leuven studies were single-center trials, multicenter studies were set up to test whether TGC could be applied in daily practice in the ICU. A dose−effect relationship was described between the average range of BG and mortality in a post hoc analysis [52]. In contrast, the mortality rates did not differ between the IIT group and the conventional group in the Volume Substitution and Insulin Therapy in Severe Sepsis study [19]. In the GluControl trial [17], the mortality did not differ between the randomly assigned groups and in the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation [16], tight BG control was associated with an increase of the 90-d mortality from 24.9% to 27.5%.

Finally, glucose control in ICU patients was found to be beneficial in terms of mortality and morbidity in the oldest meta-analysis [53] but was without effect in the most recent meta-analysis [19]. As shown by Marik et al., these disparate findings could be explained by differences in the caloric intakes between the studies; the high caloric intake by the parenteral route was used during the Leuven studies, but not in any of the other centers [19].

The comparability between the RCTs is further hampered by differences in the monitoring technology, frequency of sampling, increasing the likelihood of "missed" hypoglycemic and hyperglycemic events (Table 1).

Current recommendations

European (the French Society and Anesthesia an Intensive Care and the French-speaking Society for Intensive Care) and American experts (the ADA/American Association of Clinical Endocrinologists [AACE]) developed panel consensus recommendations [54,55]. Excluding the specific problems of diabetic patients and children, with any condition (with or without diabetes), several items were analyzed including: the glycemic target in ICU, the diagnosis and consequences of hypoglycemia in ICU, glucose monitoring, and the effects of algorithms and protocols.

The European experts strongly suggest initiating insulin therapy for persistent hyperglycemia starting at a threshold of ≤180 mg/dL in adult ICU patients and keeping BG levels under control although a universally acceptable limit cannot be specified. The ADA/AACE consensus statement outlines the argument in favor of more relaxed glycemic targets, as ≤140 to 180 mg/dL for the majority of critically ill patients once insulin treatment is started. They confirmed that, because of the increased risk for hypoglycemia, strict glycemic control cannot be a universal strategy regardless of the condition of the patient and the training of the team. They also strongly suggest using continuous intravenous insulin as the only strategy permitted to efficiently control BG while decreasing the risk for glycemic variations of large variations in glucose in ICUs. They insist that hypoglycemia (<40 mg/dL) should be detected, even in the absence of warning clinical signs, using a close glycemic monitoring. Because bedside point-of-care glucometers provide inaccurate measurements in critically ill patients, all present guidelines recommend not using capillary blood in this population because it produces serious errors. BG concentrations should be preferentially performed on arterial (or venous) blood samples using classical laboratory devices or blood gas analyzers. The experts recommend using dynamic-scale algorithms that take a wide variety of factors into account such as the ongoing insulin delivery rate, monitoring interval, and glucose intake. Various

computer-guided protocols have been developed for this approach, including the Stochastic TARgeted (STAR) approach [56], the LOGIC-Insulin algorithm [57], enhanced model predictive control (eMPC) algorithm [58], Glucose Regulation for Intensive care Patients (GRIP) [59], and the Glucosafe, and Contrôle Glycémique Assisté par Ordinateur (CGAO) [20]. These systems, although the protocols are more complex, have the advantage of being more physiologically relevant and can adapt to inter- and intrapatient variability, including issues of insulin sensitivity, nutrition, and concomitant medication. Recently, Dubois et al. demonstrated the benefit of using the LOGIC-Insulin algorithm rather than BG control by expert nurses without increasing hypoglycemia, in a RCT of a mixed critically ill population [60]. Nevertheless, the advantages of software-guided algorithms for insulin dosing should be confirmed in large-scale trials [61].

Perspectives

Personalized treatment

As the glucose story has unfolded, it has become apparent, as in many other areas of intensive care, that one size does not fit all. Different types of patients may have different needs in terms of glucose control, making it difficult to demonstrate overall benefit in large heterogeneous trials. As examples, two additional categories of patients may differ from other types of patients: patients with chronic hyperglycemia or poorly controlled diabetes and patients in the neuro-ICU.

Few studies have examined the effects of SH and TGC in critically ill patients with diabetes and, to our knowledge, there are currently no data from interventional RCTs that have specifically studied this population. A post hoc analysis of the patients enrolled in both Leuven studies revealed the lack of benefit of IIT in patients with diabetes [52]. Similarly, observational data suggest that the independent association of hyperglycemia with mortality in the critically ill is robust in patients without diabetes but not so in those with diabetes [14,30], supporting the concept of a "diabetes paradox" [62]. Existing data from other studies suggest that the optimal BG target may be higher in patients with pre-existing diabetes than in those without [32,63]. Other work has demonstrated that a long duration of time in range (70–140 mg/dL) is independently associated with survival in patients without diabetes but not in those with diabetes [64]. In addition to differences between patients with and without diabetes, there also may be differences depending on the degree of premorbid glycemic control in patients with diabetes [65]. Indeed, the glycemic threshold at which the counterregulatory mechanisms to control BG concentrations are activated is higher in patients with poorly controlled diabetes than in those with well-controlled diabetes or without diabetes. However, further study is needed to define the optimal level because levels that are too high also may be associated with complications, such as infection.

Brain-injured patients are particularly sensitive to BG variations as the brain has high-energy requirements and limited glucose reserves. Hypoglycemia can cause secondary brain injury, thus it should especially be avoided in these patients. However, hyperglycemia also can enhance brain injury and various observational studies have demonstrated increased mortality associated with hyperglycemia in patients with traumatic brain injury (TBI) and intracerebral hemorrhage [66,67]. Several prospective trials have compared TGC and "conventional" glucose control protocols in patients in the neuro-ICU [68,69]. Most of these studies reported increased rates of hypoglycemia in patients in the TGC group with little or no effect on mortality or neurologic outcomes, although some reported reduced infection rates with TGC. Given the negative effects of hypoglycemia on secondary brain injury, depending on its severity and duration, the traditional cutoff values for hypoglycemia may need to be reconsidered in these patients.

As the metabolic response to stress includes three phases, each characterized by distinct adaptive mechanisms, optimal targets for glycemic control may vary over time. Interestingly, in a retrospective analysis, Meier et al. reported that a BG target of 63 to 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 to 144 mg/dL, whereas in the second week the lower target seemed more beneficial [70]. Therefore, it may be that glucose concentrations should be kept at higher levels during the early phase of TBI, and possibly in other acute neurologic conditions, and lower targets used at later stages. Further study is needed to clarify this issue.

Continuous glucose monitoring

As with other parameters that are regularly monitored in the ICU, the concept of continuous monitoring was advanced for BG. The glycemic control with insulin to maintain BG in a narrow range as currently recommended involves repeated check of BG and increases dramatically the workload of the nursing staff. Moreover, performance of glucose control may be highly variable as it depends on several methodological aspects: technique of BG measurement, delivery of insulin, efficacy of glucose control algorithm, and the commitment and expertise of nursing staff [71]. Hence, the use of intravascular continuous glucose monitoring (CGM), when combined with a validated insulin infusion protocol that minimizes glycemic variability, could offer benefit compared with intermittent monitoring systems, enabling insulin infusions to be adjusted more rapidly and potentially more accurately because trends in BG could be more readily identified and episodes of hypoglycemia avoided [72]. The three predominant techniques currently used for CGM in the ICU involve glucose oxidase, mid-infrared spectroscopy, and fluorescence. The degree of invasiveness of a CGM technique varies from highly invasive (intravascular devices) through the minimally invasive subcutaneous techniques, to non-invasive transdermal devices. There is now ample evidence to support the use of CGM devices as means of facilitating glucose control and decreasing nursing workload in ICU patients. Yet, they remain largely experimental in the ICU because many devices failed to meet the mean absolute relative difference point accuracy standard [73].

Closed-loop systems

The ultimate innovation in the field could be the development of closed-loop systems that mimic an artificial pancreas. In such technique (artificial pancreas), CGM measurements can be fed into computerized systems, which then adapt the insulin or glucose infusion rate accordingly, taking into account specific patient- and treatment-related variables. Several studies have now evaluated use of closed-loop systems in critically ill patients. Okabayashi et al. evaluated a closed-loop glycemic control device in 447 surgical ICU patients and reported that the glucose concentration was kept in target for 96.8% in the intermediate glucose control group and 85.8% in the intensive glucose control group [74]. No patients in either group became hypoglycemic (<40 mg/dL) during the study period. Further clinical studies are needed to determine whether this effect can influence outcomes.

Conclusions

SH during critical illness involves complex interactions between some counter-regulatory hormones, adipokines, and inflammatory cytokines causing both excessive and non-inhibitable production of glucose by the liver and IR of the IMGU tissues. Extensive observational data have shown a consistent relationship between BG levels in hospitalized patients and adverse clinical outcomes. However, the optimal target for glycemic control in the ICU remains debated, despite the publication of several RCTs comparing different glycemic target ranges for insulin therapy. Therefore, an intermediate glycemic target is preferred. Current international guidelines regarding glycemic management of intensive care patients advocate initiating insulin infusions for BG measurements >180 mg/dL. Research work is ongoing to determine whether different types of patients (e.g., poorly controlled diabetes and neuro-ICU patients) may have different needs in terms of glucose control and could therefore benefit from personalized glycemic control.

In terms of BG, CGM may, by facilitating more timely therapeutic intervention, potentially help to better control the three domains of dysglycemia (hyper- and hypoglycemic episodes, and also reduce glucose variability) that have been shown to be factors independently associated with increased risk for mortality in critically ill patients. The next step is to clearly demonstrate that the better glucose control achieved with CGM or closed-loop systems is associated with improved clinical outcomes compared to intermittent monitoring and with a favorable cost-benefit ratio.

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