Hyperglycemia in the Surgical Intensive Care Unit

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Introduction

The hyperglycemic response to critical illness has been known since Claude Bernard first described hyperglycemia during hemorrhagic shock in 1878 [1]. Since then, numerous studies in critically ill patients have shown a strong association between the severity of the hyperglycemia and the risk of morbidity and mortality [2, 3]. Whether this association merely reflects the severity of disease/surgical stress or whether hyperglycemia negatively affects outcome remained unanswered for decades. In 2001, a landmark randomized clinical study performed in 1548 surgical critically ill patients showed that lowering blood glucose levels to normoglycemia (80–110 mg/dl) reduced intensive care unit (ICU) and hospital mortality, as well as morbidity [4]. These findings support a causal relationship between hyperglycemia and poor outcome in critically ill patients. Several studies subsequently designed to confirm these findings were, however, not able to replicate these results, fuelling the controversy about the role of glycemic control in the ICU. In this chapter, we review the incidence, pathophysiology, and management of hyperglycemia in the ICU, with focus on the surgical ICU.

Stress Hyperglycemia

Definition

The vast majority of adult patients undergoing major surgical or disease-related stress develop "stress hyperglycemia"[5]. Although any blood glucose value higher than the normal healthy reference is "hyperglycemia," a definition of stress hyperglycemia has been put forward as any blood glucose value above 140 mg/dl during illness, mostly restricted to patients without previous evidence of diabetes [6]. However, a worsening of hyperglycemia during stress/illness in patients with pre-existing diabetes also reflects "stress hyperglycemia," but no cutoff levels have been published for this particular population.

Incidence and Relation to Outcome

Among the other metabolic responses to severe stress, hyperglycemia is one of the most common. In a prospective observational study, as many as 90 % of critically ill patients developed hyperglycemia/insulin resistance while in ICU [7].

It was believed that a moderate hyperglycemic response to stress could provide glucose to cells that predominantly rely on glucose as metabolic substrate without the need of insulin for glucose uptake, such as neurons and blood cells. Therefore, this metabolic response was long assumed to be adaptive and beneficial. This dogma in medicine, based on assumption and rationale, remained untested for more than a century.

However, this viewpoint contrasted with data that correlated the severity of "stress hyperglycemia" in critically ill patients with an increased risk of morbidity and mortality [2, 3, 8–10]. The association between blood glucose levels and mortality risk follows a J-curved relationship with the lowest risk in the "normal-for-age" range (Fig. 36.1) [11]. For the adult critically ill patient this generally means a fasting blood glucose level between 80 and 110 mg/dl. In critically ill patients with pre-existing diabetes mellitus, however, the nadir is shifted to higher blood glucose levels. In the hyperglycemic range there is a quasi-linear relationship between blood glucose levels and mortality risk, but this curve is blunted in critically ill patients with pre-existing diabetes mellitus.

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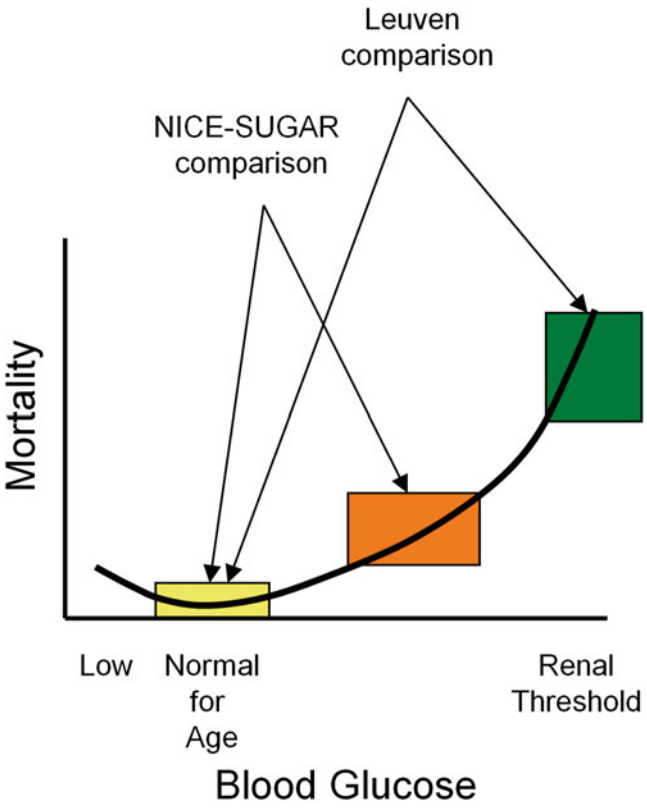

Fig. 36.1 The association between blood glucose levels and mortality risk follows a J-curved relationship with the lowest risk in the "normal-for-age" range. The target level for the control groups in the Leuven studies and in NICE-SUGAR differed substantially. Reproduced from Van den Berghe G, et al. Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab 2009; 94:3163–3170 with permission from The Endocrine Society [57]

Pathophysiology

Several factors are involved and interact in the development of hyperglycemia in the critically ill patient. These include the patient's predisposition, the pathophysiology of stress hyperglycemia and treatments.

Predisposition may be reflected by the patient's pre-morbid status such as body composition and co-morbidities like obesity, prediabetes and pancreatic function (e.g., Whipple operation) [5]. The pathophysiology of stress hyperglycemia is complex. The surgical or illness-related stress will trigger neuroendocrine and inflammatory/immune stress responses which lead to the typical upregulation of counter-regulatory hormones, such as catecholamines, glucagon, growth hormone and cortisol, as well as cytokines (e.g., tumor necrosis factor (TNF)-alpha and interleukin-1) [12]. It is currently believed that a complex interplay between the counter-regulatory hormones leads to an increase in endogenous glucose production and insulin resistance, which in turn lead to hyperglycemia. High levels of glucagon, epinephrine, and cortisol stimulate glycogenolysis and gluconeogenesis in the liver, thus enhancing endogenous glucose production (Fig. 36.2) [13–15]. Stimulated hepatic gluconeogenesis is believed to be the most important factor contributing to stress hyperglycemia [16]. The same counter-regulatory hormones induce a state of insulin resistance, mediated by dysfunction of post-receptor insulin signaling and downregulation of glucose transporter (GLUT)-4 [17, 18]. This results in a reduced insulin-mediated glucose uptake in skeletal muscle and the heart. Furthermore, the exercise-stimulated glucose uptake in skeletal muscle is

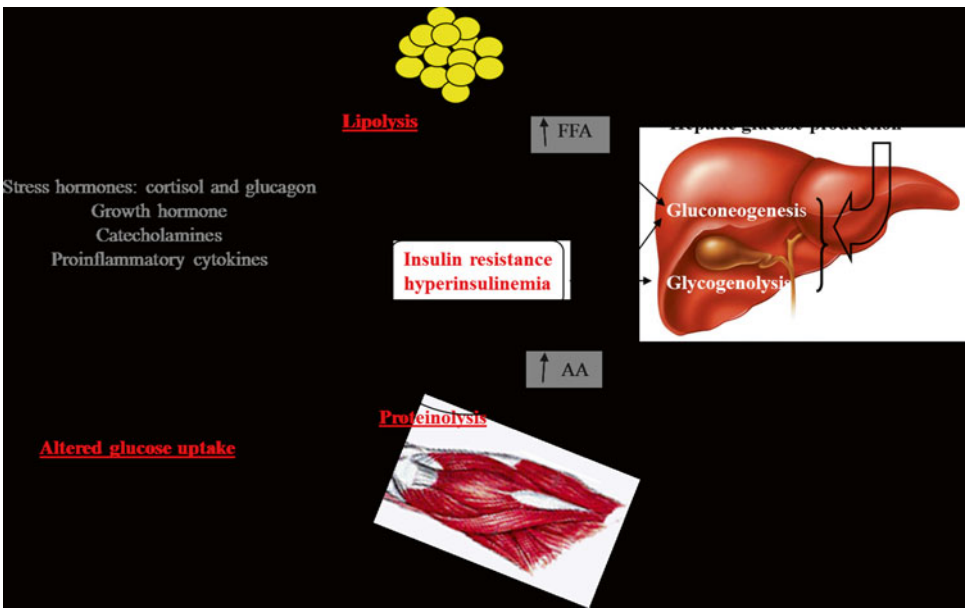

Fig. 36.2 Mechanisms of stress hyperglycemia. *AA* amino acids, *FFA* free fatty acids. Reproduced from Derde S et al. Insulin treatment in intensive care patients *Horm. Res. 71, 2-11 (2009)* with permission from S. Krager AG, Basel [88]

likely abolished in view of the immobilization of the patient. Nevertheless, whole-body glucose uptake during stress hyperglycemia is increased, due to enhanced glucose uptake in various tissues, like brain and blood cells, by glucose transporters that do not need insulin for glucose uptake [19–21]. High levels of circulating glucose aggravate the inflammatory response, which in turn can further increase insulin resistance and endogenous glucose production, potentially leading to a vicious cycle whereby hyperglycemia fuels more severe hyperglycemia [22, 23]. Finally, several treatments used during ICU stay may disturb glucose homeostasis, including the administration of glucocorticoids, total parenteral nutrition, glucose infusion, and vasopressors.

Glycemic Control in the Intensive Care Unit

Stress hyperglycemia has been tolerated in the ICU for decades, as it was believed to be a beneficial, adaptive response. Until 2001, the standard care consisted of starting insulin administration only when blood glucose levels exceeded the renal threshold (215 mg/dl), since such high levels were expected to evoke glycosuria-induced hypovolemia. As already stated, however, this view contrasted with observational data showing a strong association between hyperglycemia and death. Such correlation between hyperglycemia and risk of death may merely reflect the severity of the disease or, alternatively, hyperglycemia may induce excess harm. To differentiate between both possibilities, a first randomized control trial (RCT) was performed.

Leuven Landmark Studies

The first RCT to test the hypothesis that hyperglycemia in the ICU contributes to excess harm was performed in 2000 in Leuven, Belgium [4]. In this RCT, 1548 adult patients admitted to the surgical ICU of a single hospital were randomized into two arms. In the intervention arm, patients received intravenous insulin to achieve a normal blood glucose level (80–110 mg/dl) during their stay in the ICU, which was called "intensive insulin therapy (IIT)." In the control arm, patients did not receive insulin unless glucose levels exceeded 215 mg/dl, which was the standard care at the time ("conventional insulin therapy," CIT). All patients received early supplemental parenteral nutrition when enteral nutrition was insufficient, according to the European guidelines at the time [24]. The study was stopped early after a pre-planned interim analysis because of determination of inferiority in the control group. The IIT intervention lowered ICU mortality by an absolute 3.4 % (8.0–4.6 %) in an intention-to-treat analysis. Importantly, with the 1548 patients included at that time, the study had a statistical power of 79 % to detect the observed ICU mortality difference between the two groups. Similarly, in-hospital mortality was reduced by 3.7 % (10.9 to 7.2 %). IIT also resulted in less morbidity, reflected by a lower incidence of acute kidney failure, hyperbilirubinemia, severe infections and critical illness polyneuropathy, as well as a shorter duration of mechanical ventilation. The clinical benefits were more pronounced among long-stay patients and were mostly explained by the lowering of blood glucose levels and not by the infusion of insulin per se [25–27]. The short-term survival benefit was maintained after 4 years [28].

The IIT intervention was further investigated in the Leuven medical ICU (MICU) and the pediatric ICU (PICU), which largely confirmed the beneficial effects of glycemic control in the surgical ICU [29, 30]. The study performed in the MICU was powered to detect a significant effect on mortality among long-stay patients, for which it was indeed confirmed, but the study also unintentionally had a short stay population and thus the lower mortality in the intention-to-treat population did not reach statistical significance [29, 30]. Nevertheless, organ-protective effects and shorter duration of mechanical ventilation and ICU stay were also documented in the total MICU population [29, 30]. The third Leuven study performed in the PICU comprised a predominantly surgical patient population, targeted normal fasting glucose levels for each age group (50–80 mg/dl in infants and 70–100 mg/dl in children), and showed similar mortality and morbidity benefits as seen in the adult SICU [30].

Several mechanistic studies were subsequently performed to unravel how IIT may exert such pronounced beneficial effect on morbidity and mortality. As mentioned, lowering of glycemia rather than the infusion of insulin appeared most important for improving outcome, as shown by *post hoc* analysis of the Leuven surgical study [26] and an experimental study in critically ill rabbits [27]. IIT lowered glycemia by shuttling glucose into skeletal muscle and adipose tissue [31, 32], hereby preventing cellular glucose overload in tissues that take up glucose without the need of insulin, such as the liver, nervous system, endothelium, and immune cells. Preventing cellular glucose overload protected against endothelial dysfunction [27, 33, 34] and mitochondrial failure [35–37], two major pathways implicated in organ failure in critical illness [38]. IIT also lowered excessive inflammation as illustrated by lower levels of C-reactive protein [39]. Furthermore, IIT improved dyslipidemia and lowered total and free cortisol levels during critical illness [31, 40]. Importantly, IIT also largely prevented the development of neuropathological abnormalities [41]. All these effects might have contributed to the beneficial impact of IIT during critical illness.

Multicenter Confirmation Studies

An observational before/after study in 800 mixed medical/surgical ICU patients demonstrated improved survival, a lower incidence of new kidney injury, fewer patients needing red blood cell transfusion and a shorter length of ICU stay with implementation of IIT [42]. Several smaller single center studies also reported clinical benefits of IIT as seen in the Leuven landmark studies [43–46], whereas two other studies did not [47, 48]. Subsequently, several multicenter studies were performed aiming to test whether the Leuven results could be reproduced outside the well-controlled setting of a single-center study.

The Glucocontrol RCT included 1101 adult mixed surgical (59 %) and medical (41 %) ICU patients from 21 participating centers [49]. The blood glucose target in the control group of this study was 140–180 mg/dl, which differed from the target used in the Leuven trials (180–200 mg/dl). The study was stopped early because the glycemic control could not be reached in the intervention group and because the incidence of hypoglycemia was deemed too high (9.8 %). The study did not show any significant effect on mortality or morbidity. The VISEP trial included 488 adult general ICU patients (53 % surgical patients) from 18 participating centers [50]. The VISEP trial was designed as a four-arm study to assess the efficacy of fluid resuscitation (10 % pentastarch vs. modified Ringer's lactate) and glucose control (IIT vs. "usual care," presetting similar targets as in the Leuven studies) in patients with severe sepsis and septic shock. This study was stopped early because of the high incidence of hypoglycemia (12.1 %) in the intervention group. Again, there was no significant effect on mortality, nor on morbidity. The COIITSS trial is another study with a 2 by 2 design and included patients from 11 centers. The study simultaneously assessed the efficacy of insulin therapy and the combined administration of hydrocortisone and fludrocortisone in 509 adult patients with sepsis and also did not find any benefit of insulin therapy [51]. The NICE-SUGAR trial included 6104 general ICU patients, of which 37 % were surgical patients, from 42 participating centers [52]. The blood glucose target in the control group of this study was 144–180 mg/dl, which differed from the target used in the Leuven trials (180–200 mg/dl). In this study IIT did not affect morbidity, but increased mortality from 24.9 to 27.5 %.

Recently, two RCTs on glycemic control with insulin have been performed in critically ill children. The SPECS two-center study on 980 children undergoing surgery with cardiopulmonary bypass did not find any benefit of targeting blood glucose levels of 80–110 mg/dl versus conventional glucose management [53]. The CHiP trial included 1369 children, of which 60 % cardiac surgery patients, who were admitted to the PICU from 13 centers in England [54]. The blood glucose target in the intervention arm was 72–126 mg/dl, compared to conventional glycemic control, with a target level below 216 mg/dl. This study showed no effect on mortality, despite an increase in hypoglycemia in the IIT group, but IIT reduced the incidence of kidney failure, length of stay in the hospital and the costs of hospital and community health services.

At first glance, the different clinical trials on IIT in ICU yielded contradictory results, which sparked a fierce debate on glycemic control in the ICU. Therefore, it is very important to take a closer look at the differences between the studies to find a possible explanation for the apparently conflicting results. Important differences among the studies are therefore discussed in the following section.

Concerns and Pitfalls

Patient Population

The proof-of-concept Leuven study was performed in the surgical ICU, whereas the confirmation studies were performed in general/mixed ICUs. Preventing hyperglycemia in surgical critically ill patients could theoretically avoid hyperglycemia-induced organ failure, whereas in the medical or mixed ICU a greater fraction of the patients is admitted with already established organ failure, reducing the therapeutic effect of glycemic control [25, 55]. This was supported by a meta-analysis that found overall benefits of IIT in the surgical ICU setting but not in the general or medical ICU [56].

Targeted Glucose Range

The so-called confirmation studies used different glycemic target ranges and achieved a different level of glucose control than the Leuven studies. The Leuven studies compared targeting normoglycemia (80–110 mg/dl) with an approach where blood glucose levels were left untreated up to 215 mg/dl as the renal threshold. Most confirmation trials compared targeting normoglycemia with an intermediate glucose target (140–180 mg/dl) and hence labeling them as confirmation trials is not correct, as indeed a benefit could already have occurred by targeting intermediate blood glucose levels in the control group (Fig. 36.1) [49, 52]. Furthermore, the therapy compliance in the studies differed significantly. In the Leuven landmark trial the targeted glucose level was reached in more than 70 % of the patients and glucose levels in both groups were well separated with hardly no overlap between the 2 study arms for the level of blood glucose reached in the patients [57]. In the NICE-SUGAR trial, for instance, compliance was much less than 50 %, which resulted in a significant overlap (>50 %) between the two groups, further

compromising the value of this study as testing the hypothesis of a benefit from preventing hyperglycemia [57].

Statistical Power

In order to detect a certain difference in clinical outcome between groups in a RCT, the sample size should be sufficiently high to reach adequate statistical power. This is problematic in several studies on IIT in the ICU. For instance, the VISEP study was designed to detect a difference of 1.2 in SOFA score with 80 % power [50]. The study was prematurely stopped after inclusion of 488 of the 600 planned patients. IIT is not expected to reduce the primary endpoint of 28-day mortality and the study only permitted the detection of an unrealistically high 10 % absolute reduction of the secondary endpoint of 90-day mortality and, hence, was underpowered by a factor of more than 10 [58]. Even the NICE-SUGAR study, the largest study performed so far, was in fact underpowered [52, 57]. Indeed, power calculation was based on an absolute decrease in mortality of 3.8 % based on the Leuven studies. However, with the blood glucose target ranges being much closer to each other than in Leuven, only a 1–1.5 % mortality reduction could be expected, based on *post hoc* analysis of the Leuven data [26]. Demonstrating this smaller difference would require inclusion of 70,000 patients [57]. Also the CHiP trial was underpowered due to overestimation of the expected effect size, as only about half of the patients in both groups in fact received a different study intervention, and the difference in blood glucose level between the study groups was so low that it may not have been clinically relevant [59]. The lack of sufficient statistical power in these studies may offer an explanation why these studies did not notice any positive effect on mortality.

Glucose Measurement

The glucose sampling site and the glucose measurement tools differed between the studies. In the Leuven proof-of-concept studies, glucose measurements were performed on arterial blood with a blood gas analyzer. Subsequent studies, however, used different sampling sites (venous, arterial, and capillary blood) and a variety of measurement techniques, including handheld point-of-care glucose meters. Several studies have shown that capillary sampling in critically ill patients, especially in those who are hemodynamically unstable and are being treated with vasopressors, generate imprecise glucose values [60, 61]. Several handheld glucometers, such as those that were used in the NICE-SUGAR study, were shown to be too inaccurate to safely target a narrow range of blood glucose [62, 63]. Furthermore, modeling studies have shown that using such an imprecise glucose meter may evoke a dramatic increase in glucose variability and undetected hypoglycemia, two factors that have been associated with adverse outcome [64, 65]. The use of a blood-gas analyzer also provides simultaneous measurement of potassium in each sample [57]. This is of major importance when treating the ICU patient with insulin, because insulin can induce iatrogenic hypokalemia with subsequent life-threatening arrhythmia. Remarkably, in the NICE-SUGAR study, the excess mortality was attributed to an increase in cardiovascular deaths. In this study, the least accurate technique with the highest chance of hypokalemia (measuring capillary blood with handheld glucometers) was commonly used. Recently, a consensus guideline was published advocating analysis of arterial blood with a blood gas analyzer in critically ill patients [66].

Hypoglycemia and Glycemic Variability

Treating hyperglycemia in the ICU with insulin inevitably increases the risk of hypoglycemia, as uniformly found in all RCTs that studied this intervention [4, 50, 52]. This has been a topic of considerable debate. Whereas it is commonly accepted that prolonged and severe hypoglycemia can have grave consequences and may even result in death, it is not clear whether short-lasting, iatrogenic hypoglycemia in the ICU setting induces excess harm with a deleterious effect on outcome [6].

In the Leuven studies, the incidence of hypoglycemia in the IIT group rose from 0.8 to 5.1 % in SICU patients, from 3.1 to 18.7 % in MICU patients and from 1.4 to 24.9 % in PICU patients [4, 29, 30]. Nevertheless, such hypoglycemia was never associated with immediate mortality. Patients who developed hypoglycemia did have an increased mortality risk, but this risk was higher with spontaneous than with iatrogenic hypoglycemia [67]. This suggests that hypoglycemia is a sign of severity of illness and for this reason correlated with mortality. This constellation is further supported by a study of circulating neurological damage markers in the children of the Leuven PICU study. Indeed, in patients experiencing a brief hypoglycemic episode these markers were already elevated before the hypoglycemic event [68]. The most convincing evidence that iatrogenic short-lasting hypoglycemia did not induce excess harm was presented by the long-term follow-up of these children. Importantly, children who received IIT during intensive care did not score worse on any measure of intelligence and actually performed better for motor coordination and cognitive flexibility 4 years after ICU admission, despite the higher incidence of hypoglycemia [69]. This suggests that hyperglycemia is more detrimental to the brain, which is further supported by neuropathological studies in brain biopsies of

critically ill patients and animals [41]. Progressive neural damage has also been observed in hyperglycemic mice after spinal cord injury, impairing functional improvement, which can be rescued by glycemic control [70]. Hyperglycemia has been identified as an independent predictor of poor functional outcome of spinal cord injury patients, but randomized clinical studies on IIT in this patient population are currently lacking [70].

Even though short-lasting hypoglycemia most likely does not induce excess harm, severe hypoglycemia clearly should be avoided as much as possible. Therefore, it is important to frequently measure glycemia. Studies have shown that extending glucose intervals beyond 2 h appears to increase the risk of serious hypoglycemic events [71]. However, many studies prescribe increasing the measurement intervals (as long as 4–6 h) when glucose has "stabilized," which may increase the likelihood of a serious hypoglycemic event.

Another point of interest is glucose variability. Glucose variability appears closely associated with death, whether the patients are being treated with tight glycemic control or not [72–75]. Factors contributing to glycemic variability are poorly characterized, but most likely include intrinsic and extrinsic patient factors. Extrinsic factors most likely include nutritional support, mode of insulin administration and glycemic control algorithm. It is possible that glycemic variability could have contributed to the different outcomes in the studies, since protocols differ significantly in their ability to keep patients within the desired range [76]. The fact that in the Leuven studies rebound hyperglycemia after hypoglycemia was carefully avoided may be a very important aspect in this regard [30]. Indeed, hyperglycemia after hypoglycemia may be more detrimental rather than the hypoglycemic event itself [77].

With the aim of minimizing hyperglycemia, hypoglycemia, and glucose variability, a lot of research is being done on continuous glucose measurement tools and non-insulin glucose-lowering drugs [78, 79].

Nutritional Support

The patients enrolled in the proof-of-concept studies all received early supplemental parenteral nutrition if enteral nutrition was insufficient, according to the European guidelines at the time [24]. This contrasted with the NICE-SUGAR trial where the patients were fed virtually exclusively via the enteral route during the first week in ICU while accepting a caloric deficit, following the American/Canadian guidelines [80, 81].

Interestingly, a large multicenter RCT was performed, called the EPaNIC study, which compared both feeding strategies [82] and theoretically may reconcile the findings of the Leuven studies versus the NICE-SUGAR study. In this study, 4640 critically ill patients were randomly allocated to either early or late initiation of parenteral nutrition, while targeting normoglycemia. Patients who were allocated to the late-initiation group only received parenteral nutrition if enteral nutrition was still insufficient on day 8 in the ICU, whereas patients allocated to the early-initiation group received parenteral supplementation within 48 h of ICU admission. Remarkably, accepting a caloric deficit by withholding parenteral supplementation did not affect mortality but markedly accelerated recovery. This was reflected by a lower incidence of new infections, less muscle weakness, less liver dysfunction and reduced need for renal replacement therapy, as well as a reduced duration of mechanical ventilation and stay in ICU. A mechanistic study implicated an important role of suppression of autophagy activation in the worse outcome with early parenteral nutrition [83]. Autophagy is an essential cellular housekeeping system that is responsible for the clearance of damaged organelles, other cellular constituents, as well as microorganisms [84]. Taking into account the severe damage that is inflicted to mitochondria and functional proteins under hyperglycemia [35, 37], which normally should be removed by autophagy, it may be inferred that the nutritional regimen contributed to the different outcomes in the Leuven and NICE-SUGAR studies. More particularly, cellular damage evoked by moderate hyperglycemia may be sufficiently cleared when autophagy activation is adequately preserved in case of a significant caloric deficit under late initiation of parenteral nutrition as in the NICE-SUGAR study. Addressing this hypothesis would of course require a new adequately powered RCT in the setting of late initiation of parenteral nutrition. The number of patients who experienced hypoglycemia in the EPaNIC study was slightly higher in the late-initiation than in the early-initiation group [82]. The strategy of late initiation of parenteral nutrition when enteral intake is insufficient, in combination with inadequate glucose monitoring may lead to an increased risk of severe hypoglycemia, which may be another aspect to consider in the adverse outcome with IIT in the NICE-SUGAR study.

Practical Recommendations

Since the publication of the Leuven landmark study in 2001, there is an increased interest in glycemic control in the ICU. Whereas the proof-of-concept studies showed a possible substantial benefit of this strategy, the implementation studies clearly showed the complexity of introducing this strategy in daily practice in various ICUs around the world. Several important aspects need to be considered for safe implementation of glycemic control, independent of the targeted glucose range. Therefore, the following conditions should be met:

- Measure glucose levels with a standardized blood glucose measurement tool.

The analysis of arterial blood with on-site blood gas analyzers is the standard-of-care [66]. A handheld blood glucose meter with an acceptable error range with use of arterial or venous blood may be an alternative. Capillary blood samples are unreliable.

- Perform frequent blood glucose measurements and titrate insulin infusion by trained staff.

A standardized blood glucose control algorithm should be used and blood glucose levels should be measured best every 2 h and at least every 4 h. Thorough training of the ICU health care providers (physicians and nurses) in the execution of glycemic control improves patient safety.

- Apply the right mode of insulin administration.

Infuse insulin intravenously in a continuous manner via a central venous catheter using a dedicated lumen and accurate syringe pumps. Subcutaneous insulin administration should not be used in the ICU.

Hyperglycemia in the Diabetes Patient

The prevalence of diabetes is rising worldwide, especially in the western world. For example, the prevalence of diabetes in the USA increased from 8.3 % in 2010 to 9.3 % in 2012. As a consequence, the number of ICU patients with pre-existing diabetes will increase. Therefore, it is important to discuss glycemic control in the patient with pre-existing diabetes, because different rules may apply for glycemic control in the ICU for these patients.

Several studies have shown that the association of hyperglycemia with increased risk of mortality in ICU was much stronger among patients without pre-existing diabetes than among individuals with diabetes, the latter group showing a "J-curve" that is flatter and shifted to the right [85–87]. A possible explanation for this finding is that diabetes patients develop a tolerance to a degree of hyperglycemia when not tightly controlled and readjust to new "normal" levels of glycemia, which are higher than for healthy nondiabetic patients. Targeting normoglycemia in the ICU in such patients with diabetes may actually reflect an acute change and derangement of this new homeostasis and may therefore induce harm. Targeting a mean blood glucose level of 80–110 mg/dl in these patients appeared associated with no benefit or even an increase in mortality [85]. Furthermore, glycemic variability appeared not to be independently associated with an increased risk of mortality in patients with diabetes, unlike in patients without diabetes [85]. This might reflect a habituation of the body to fluctuating glucose levels. Nonetheless, hypoglycemia in patients with diabetes remains a major concern, so it is advised to achieve stable glucose levels in these patients to minimize the chance of hypoglycemia.

Apparently, the concept of "one size fits all" is not applicable for glycemic control in the ICU and it may be advisable to tolerate or target mild hyperglycemia in patients with diabetes, since these levels are the levels the patients were exposed to before critical illness.

Conclusion

For more than a century stress hyperglycemia has been considered a beneficial response, based on theoretical considerations rather than on experimental data. The Leuven landmark study in 2001 challenged this traditional view, clearly showing a negative effect of severe hyperglycemia during critical illness. Subsequent studies, trying to replicate these findings, showed mixed results, which emphasize the complexity of stress hyperglycemia and the complexity of implementing glycemic control in the ICU.

Based on the available data, refraining from early parenteral nutrition and thus tolerating an early substantial caloric deficit in combination with targeting normoglycemia appears the most evidence-based strategy for preventing additional metabolic damage to the critically ill patient, especially for the surgical critically ill patient. Nonetheless, in settings where the logistics to achieve proper glycemic control are not available, tolerating mild hyperglycemia while not feeding early, may be a defendable option, based on common sense. In case of patients with diabetes, it may be better to tolerate mild hyperglycemia, instead of targeting normoglycemia, and for these patients proper logistics should also be applied, to minimize the chance of hypoglycemia.

Glycemic control in the ICU is an evolving and exciting field in which extensive research is done. Further studies are needed to increase insight and further optimize clinical practice in the future.

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