Insulin Treatment in Intensive Care Patients

Sarah Derde Ilse Vanhorebeek Greet Van den Berghe

Department of Intensive Care Medicine, Katholieke Universiteit Leuven, Leuven, Belgium

Key Words

Critical illness • Hyperglycemia • Hypoglycemia • Insulin • Metabolism

Abstract

Hyperglycemia is a major risk factor for increased morbidity and mortality in the intensive care unit. In two large randomized controlled single-center studies, the maintenance of strict normoglycemia with intensive insulin therapy has been shown to reduce morbidity and mortality. The benefits were more pronounced with at least a few days of treatment. Several implementation studies confirmed that blood glucose control with intensive insulin therapy is beneficial for critically ill patients. Two studies planned as large randomized controlled trials evaluating the effect of glycemic control in adults were stopped prematurely because of protocol violation and/or increased risk of hypoglycemia. The only multicenter trial designed with sufficient statistical power to assess the impact of strict blood glucose control with intensive insulin therapy on survival of a heterogeneous adult critically ill patient population is still ongoing. While awaiting these results, the current evidence favors strict control of blood glucose levels to normoglycemia below 110 mg/dl. Avoiding glucose toxicity appears crucial to obtain the clinical benefits of this therapy, although direct insulin effects may contribute as well.

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Introduction

Critical illness is any condition in which the patient requires mechanical aid or pharmacological agents to support failing vital organ functions. Because of the evolution of intensive care medicine during the past decades, patients are now able to survive diseases and trauma that were previously lethal. They frequently enter a chronic phase of critical illness during which they remain dependent on vital organ support for a more or less prolonged period.

A variety of nonspecific metabolic disturbances, culminating in a hypercatabolic wasting syndrome, characterize the condition of critical illness. These include protein loss, at first sight paradoxical preservation or accumulation of fat stores, hypertriglyceridemia, hyperglycemia and insulin resistance. During the ‘unnatural’ chronic phase of critical illness, such hypercatabolism, with the excessive breakdown of proteins to mobilize amino acids as substrate for healing tissues and synthesis of acute phase proteins and glucose in the liver, leads to profound breakdown of lean body mass and puts the patient at risk for delayed recovery.

The development of stress hyperglycemia, which is common in critically ill patients and had long been considered as an adaptive and beneficial response for organs that largely rely on glucose as source of energy, is a recognized marker of adverse outcome. As shown by a large, randomized, controlled study, the use of insulin therapy

Fig. 1. Mechanisms of hyperglycemia in critical illness. AA = Amino acids; FFA = free fatty acids.

to maintain normoglycemia improves survival and reduces morbidity of patients who are in a surgical intensive care unit (ICU).

Hyperglycemia in Critically Ill Patients

Hyperglycemia commonly occurs in critically ill patients and has been identified as an independent risk factor for adverse outcome in numerous clinical settings, which include severe brain injury, trauma, myocardial infarction, and stroke [1–4]. The stress imposed by any type of acute illness or injury leads to dysregulation of glucose homeostasis with development of glucose intolerance, hyperglycemia and peripheral insulin resistance (fig. 1). A state of hepatic insulin resistance prevails, and the normal inhibition of endogenous glucose production is impaired. Indeed, although blood

glucose levels are elevated and insulin is abundantly released, the hepatic glucose production is increased. High levels of stress hormones such as glucagon and cortisol as well as of growth hormone, catecholamines and proinflammatory cytokines play a role in this increased gluconeogenesis, by increasing lipolysis and proteolysis, hence providing substrates for this pathway [5]. Glucose uptake mechanisms are also affected during critical illness and contribute to the development of hyperglycemia. The important exercise-stimulated glucose uptake in skeletal muscle is likely abolished in view of the immobilization of the patient. Insulin-stimulated glucose uptake by glucose transporter 4 (GLUT-4), present in heart, skeletal muscle and adipose tissue, is compromised [6, 7]. Nevertheless, whole-body glucose uptake is increased, accounted for by tissues that – unlike skeletal muscle – are not dependent on insulin for glucose uptake, such as brain and blood cells.

Table 1. Publications of studies on intensive insulin therapy in the ICU

Study	n	Patients	Glycemia, mg/dl	Results	Kind of study
Van den Berghe et al. [10]	1,548	surgical	153 → 103	↓ morbidity and mortality ↓ infections ↓ acute renal failure ↓ critical illness polyneuropathy ↓ liver dysfunction with hyperbilirubinemia ↓ red blood cell transfusions ↓ prolonged mechanical ventilation ↓ costs	single-center, randomized
Krinsley [14]	1,600	medical/ surgical	152 → 131	↓ mortality ↓ acute renal failure ↓ ICU stay ↓ costs	not randomized
Grey and Perdrizet [15]	61	surgical	179 → 125	↓ nosocomial infections	small randomized
Reed et al. [16]	7,261	surgical	141 → 129	↓ intra-abdominal abscesses ↓ postinjury ventilator days	not randomized
Van den Berghe et al. [17]	1,200	medical	160 → 105	↓ mortality ↓ morbidity ↓ kidney injury, hyperbilirubinemia, ↓ need for mechanical ventilation, length of stay ↓ critical illness polyneuropathy/myopathy	single-center, randomized
Glucontrol [19]	855	medical/ surgical	147 (127–163) → 118 (109–131)	target glycemic control not reached ↑ risk of hypoglycemia	randomized single-blinded
VISEP [21]	488	sepsis/septic shock	151 → 112	increased risk of hypoglycemia	randomized- multicenter
NICE-SUGAR [29]	6,100		target 144 → 108	ongoing	randomized controlled multicenter

The combined picture of higher levels of insulin, elevated hepatic glucose production and impaired peripheral glucose uptake, reflects the development of peripheral insulin resistance during critical illness [8, 9].

Insulin Therapy in the ICU

Several studies clearly associated hyperglycemia with an important risk in terms of morbidity and mortality of critically ill patients. A true causal relationship between high glucose levels and adverse outcome, however, can only be established by randomized intervention. An overview of the available randomized studies and large observational studies is given in table 1.

In 2001, Van den Berghe et al. [10] described the use of insulin to treat hyperglycemia to normalization of blood

glucose levels (80–110 mg/dl) in a large prospective randomized controlled trial performed in a surgical ICU. This landmark trial, known as the Leuven study, challenged the concept that hyperglycemia is an adaptive, beneficial response to stress that should be tolerated in critical illness. The patients in the conventional insulin therapy group received insulin only if glucose concentrations exceeded 215 mg/dl with the aim of keeping concentrations between 180 and 200 mg/dl. In the intensive insulin therapy group blood glucose levels were maintained between 80 and 110 mg/dl. Strict control of blood glucose levels with insulin reduced morbidity and mortality. In the entire study population, in-hospital mortality was significantly reduced from 10.9 to 7.2%. In the subgroup of patients who stayed in the ICU for more than 3 days, the benefit was much more pronounced, reducing mortality from 20.6 to 13.6%. Several clinical complica-

tions, such as severe infections, acute renal failure and critical illness polyneuropathy were reduced. In addition, the number of patients who acquired liver dysfunction with hyperbilirubinemia was lowered and the patients needed less red blood cell transfusions. Patients were also less dependent on prolonged mechanical ventilation and intensive care. In patients with isolated brain injury, the central and peripheral nervous systems were protected from secondary insults by this therapy, which also improved long-term rehabilitation [11]. A follow-up study of the cardiac surgery patients demonstrated improved long-term outcome with maintenance of the survival benefit of intensive insulin therapy after 4 years and without inducing more need for medical care [12]. Apart from these clinical benefits, intensive insulin therapy also substantially saved costs [13].

Following the Leuven study, the effect of implementing strict blood glucose control in a population from a mixed medical and surgical ICU was evaluated [14]. However, this study implemented a less strict glycemic control than the Leuven study, as insulin therapy reduced blood glucose levels from 152 to 131 mg/dl. Comparison with patient data before the implementation of the protocol showed a 29.3% relative reduction (from 20.9 to 14.8%) of in-hospital mortality, and a 10.8% decrease in length of stay in the ICU. Development of new renal insufficiency was 75% lower. The number of patients who acquired infections did not change significantly, but the incidence was already low at baseline in this patient group.

The beneficial effect of tight blood glucose control on the number of serious infections could, however, be confirmed in another small prospective randomized, controlled trial conducted in a predominantly surgical ICU [15]. Implementation of a glucose control protocol in a surgical trauma ICU coincided with fewer intra-abdominal abscesses and fewer postinjury ventilator days [16].

In 2006, a second large prospective randomized controlled trial was published on the effects of tight glycemic control in adult patients admitted to the Leuven medical ICU. The study was powered for demonstrating a beneficial effect on mortality for patients requiring intensive care for at least a 3rd day [17]. As in the previous Leuven study, patients were randomly assigned to receive either intensive or conventional insulin treatment. In the entire study population, intensive insulin therapy prevented morbidity but did not significantly reduce mortality. However, among the patients who stayed in the ICU for 3 or more days, i.e. the target population for which the study was powered, intensive insulin therapy reduced morbidity and mortality. The reduced morbidity with in-

tensive insulin treatment is illustrated by less kidney injury and hyperbilirubinemia, earlier weaning from mechanical ventilation and earlier discharge from the ICU and the hospital (average hospital stay 10 days shorter in this target group). Critical illness polyneuropathy and/or myopathy developed less frequently [18]. In contrast to patients in the surgical ICU, those in the medical ICU had no detectable reduction in bacteremia. However, this can be explained by the fact that sepsis in those patients is often the trigger for admission to the medical ICU.

Two studies planned as large randomized controlled trials evaluating the effect of glycemic control in adults were stopped prematurely.

In the Glucontrol study, a prospective, randomized, single-blinded trial comparing the effects of 2 glucose control strategies by insulin in ICU patients, patients were randomized to either a target blood glucose of 80–110 or of 140–180 mg/dl [19]. Participating institutions received an insulin protocol to follow, but were able to modify it as needed. The goal was to enroll 3,500 patients. However, the study was stopped in May 2006, after 1,101 patients in 21 ICUs had completed the study, because target glycemic control was not achieved and because of the increased risk of hypoglycemia.

The recently published, prospective randomized multicenter study on the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) received a lot of criticism already before publication [20, 21]. Patients with severe sepsis were randomly assigned to four arms to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy in combination with either a low-molecular-weight hydroxyethyl starch, or modified Ringer's lactate for fluid resuscitation [20, 21]. The trial of intensive insulin therapy was stopped early ($n = 488$) because of the high rate of hypoglycemia (12.1% versus 1.2% with conventional glucose management) [21, 22]. In the final report, 17.0% of the patients enrolled in the intensive insulin therapy group showed severe hypoglycemia (glucose level ≤ 40 mg/dl), compared to 4.1% in the conventional therapy group [21]. At the time of the safety analysis, reported 90-day mortality was 32.8% for the conventional and 29.5% for the intensive insulin group [22]. For the final analysis additional patients were only enrolled in the conventional group. However, 90-day mortality was now described as 35.4% for the conventional and 39.7% for the intensive group, which is very confusing. Although the trial for conventional insulin therapy was continued longer, it also had to be stopped earlier because HES therapy was associated with higher rates of acute renal failure and renal replace-

ment therapy than was Ringer's lactate. In contrast to the VISEP study, a post-hoc analysis of the Leuven studies demonstrated clinical benefits for patients with sepsis receiving intensive insulin therapy [23].

Although the infusion of insulin in combination with potassium and glucose (GIK) initially seemed to be a potentially beneficial therapy, three studies on GIK therapy after acute myocardial infarction or stroke (DIGAMI-2, CREATE-ECLA, and GIST) could not show any beneficial effect on outcome [24–26]. However, none of these trials achieved normoglycemia as glucose goal. Hence the effect of insulin therapy on outcome could not be studied and these studies only show that short-term GIK therapy without sustained blood glucose control does not work.

In a systematic review and meta-analysis of randomized controlled trials, Gandhi et al. [27] showed that perioperative insulin infusion reduces mortality and increases hypoglycemia in patients undergoing surgery but without a significant effect on other important outcomes. No or greatly varying glycemic targets were set in the original studies, however, which is a major limitation for comparing the results obtained and to draw conclusions on the efficacy of strict glycemic control with intensive insulin therapy. To this end, large randomized controlled trials with adequate glucose control are needed to confirm the mortality results.

A large randomized controlled multicenter trial, where 6,100 patients will be recruited over 35 ICUs throughout Australia, New Zealand, Canada and the USA over a 3-year period, is currently underway. In this Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, the treatment groups are assigned to one of two targets for blood glucose, intensive insulin therapy with a target of 81–108 mg/dl or conventional insulin therapy with a higher target range of 144–180 mg/dl. So far, the researchers have recruited more than 4,500 patients (October 2007) [28, 29].

While we await the results of this study, the current evidence favors the control of blood glucose levels in the ICU to below 110 mg/dl. Indeed, despite an increased incidence of hypoglycemia (vide infra), the two large Leuven trials (combined study population of 2,748 patients) not only demonstrated reduced ICU and hospital mortality but also decreased incidence of severe clinical complications, including renal morbidity, further confirmed by observational studies [14, 16, 30, 31]. Because intensive insulin therapy during intensive care is a protective strategy that prevents secondary complications, it cannot prevent damage that is already present upon ICU admission.

This may explain why the effect was more pronounced in the surgical than in the medical Leuven ICU patients.

Like in adults, the development of hyperglycemia in pediatric patients in the ICU is common. More than 80% of these patients develop blood glucose levels >110 mg/dl (6.1 mmol/l), more than 60% >150 mg/dl (8.3 mmol/l), and more than 30% exceeding 200 mg/dl (11.1 mmol/l) [32]. Positive correlations were found between the degree of hyperglycemia and risk of organ failure, length of stay in the PICU and risk of death [32–36]. Not only hyperglycemia, but also variability of blood glucose levels and hypoglycemia have been associated with adverse outcome [32].

The clinical effects of randomized intervention with intensive insulin therapy in the pediatric ICU are currently being studied [37].

Practical Aspects on Intensive Insulin Therapy in the ICU

Algorithm for Tight Glycemic Control

Although there are a lot of protocols for tight glycemic control available, strict application of an 'if-then' glucose protocol is likely not to work. Rather, the most important issue for the implementation of tight glycemic control with a continuous insulin infusion in the ICU is the training and education of the nurses. The dynamic scale protocols, combining a tight glucose target and the use of the last two blood glucose values and previous insulin doses to determine the insulin infusion rate, used by the nurses in the Leuven studies, yielded the best results [10, 17, 38].

Blood Glucose Measurement

As glucose regulation requires a quick delivery of glucose values, the nurses have to rely on bedside point of care methods instead of the golden standard central hospital laboratory measurements. A few points should be highlighted though. In the Leuven studies, glucose values were determined with the ABL blood gas analyzer and by HemoCue. When determining the glycemic target, one has to take into account whether the devices are calibrated to report plasma or whole blood values, as plasma values are generally higher [39, 40]. Also the place of sampling is important as fingerstick measurements which use capillary samples and alternative sites, such as subcutaneous adipose tissue, may not be reliable in the critically ill patient population [41, 42].

Concerns with Regard to Intensive Insulin Therapy

Hypoglycemia

Hypoglycemia occurred more often in the intensive treatment groups than in the conventional treatment groups. This observation contributed to or evoked the cessation of two trials, although similar rates of hypoglycemia were observed as in the Leuven studies. Indeed, 11% of the intensive insulin-treated patients in the Leuven studies experienced hypoglycemia compared to 10% in the Glucontrol trial; the achievement of tight glucose control was dramatically different though [10, 17, 19, 31]. Likewise, the rates for patients with sepsis were 19.6% in Leuven and 17% in VISEP [21, 23, 31]. Importantly, although hypoglycemia independently contributed to mortality in the Leuven studies in multivariate regression analysis, patients with hypoglycemia had a higher risk of death with spontaneous hypoglycemia than when it occurred after intensive insulin therapy.

In a study conducted by Vriesendorp et al. [43] on the consequences (seizures, coma, and death) of hypoglycemia in the ICU, no association between incidental hypoglycemia and mortality was found.

Nevertheless, hypoglycemia has been reported to increase neuronal death. Several events initiated by hypoglycemia have been implicated, including activation of neuronal glutamate receptors, production of reactive oxygen species, DNA damage, neuronal zinc release, activation of poly(ADP-ribose)polymerase-1 and mitochondrial permeability transition [44–48]. Interestingly, the results of a recent study on hypoglycemic neuronal death indicate that the primary source of neuronal oxidative stress after hypoglycemia and trigger of neuronal death is the neuronal NADPH oxidase, which is actually activated during glucose reperfusion, and that the rate of superoxide production and cell death is influenced by the blood glucose concentration achieved in the immediate posthypoglycemic period [45]. This illustrates how important it is, if hypoglycemia does develop, to correct it promptly but with the caution not to overcorrect.

Intensive Insulin Therapy for Less than 3 Days

In the Leuven medical ICU study, among patients treated in ICU for less than 3 days, a higher number of deaths were noted among intensive insulin-treated patients than in the conventional group. However, a post-hoc exploratory mortality analysis revealed that this observation was likely explained by selection bias. When correcting for the well-known upon-admission risk fac-

tors that are the major reasons for therapy restriction, the apparent difference in mortality disappeared [31].

High-Dose Insulin Administration to Critically Ill Patients

Multivariate logistic regression analysis identified the dose of insulin as a positive risk factor for mortality [10, 31, 49]. However, it has recently been shown that with intensive insulin therapy circulating insulin levels are only transiently higher than in conventionally treated patients, and that intensive insulin therapy actually reduces or prevents insulin resistance in the critically ill [50]. The association between high insulin dose and mortality can be explained by more severe insulin resistance in the sicker patients who have a high risk of death or, alternatively, by a true deleterious effect of hyperinsulinemia.

Intensive Insulin Therapy as Antagonist of Deleterious Effects of Parenteral Nutrition?

It was suggested that intensive insulin therapy merely serves to offset risk associated with ‘excessive’ parenteral glucose as in the Leuven studies guidelines with regard to feeding of the patients were followed that did not represent the approach adopted in many centers. The analysis of the pooled dataset of the 2 Leuven studies argued against the suggested risk of overfeeding patients. The benefit of intensive insulin therapy was independent of parenteral glucose load as mortality was lowered both in the lowest and the highest tertile of parenteral glucose load in the intention-to-treat population and in all tertiles of parenteral feeding for patients treated in intensive care for at least 3 days [31].

Metabolic and Nonmetabolic Effects of Insulin Contributing to Improved Outcome of Critically Ill Patients

Lowering Blood Glucose Levels

Critically ill patients suffer from both hepatic and skeletal muscle insulin resistance, and hence the mechanism by which insulin therapy lowers blood glucose levels in critically ill patients is not completely clear. Data from liver and skeletal muscle biopsies harvested from nonsurvivors in the Leuven study suggest that glucose levels are lowered mainly via stimulation of glucose uptake in insulin-regulated skeletal muscle. Insulin therapy increases in muscle the expression of the insulin-dependent GLUT-4, and of hexokinase-II, which is the rate-limiting enzyme of intracellular insulin-mediated glucose metabo-

lism [50]. In contrast, insulin therapy could not affect the hepatic expression of phosphoenolpyruvate carboxykinase (the rate-limiting enzyme in gluconeogenesis), and of glucokinase (the rate-limiting enzyme for insulin-mediated glucose uptake and glycogen synthesis in the liver). Also, circulating levels of insulin-like growth factor binding protein 1, normally under inhibitory control of insulin, were unaffected by insulin therapy in the total population of survivors and nonsurvivors [51]. The increased metabolic insulin signal recently observed in postmortem skeletal muscle but not in liver biopsies of intensive insulin-treated patients is in agreement with these data [52]. Taken together, this suggests that in critically ill patients exogenous insulin does not affect hepatic insulin resistance and lowers blood glucose levels mainly through stimulation of skeletal muscle glucose uptake.

Prevention of Glucose Toxicity

In normal conditions, cells respond to moderate hyperglycemia by downregulation of insulin-independent GLUT-1, GLUT-2 and GLUT-3 to protect themselves from deleterious effects [53]. However, several factors like cytokines, angiotensin II, endothelin-1, vascular endothelial growth factor and transforming growth factor- β , which are induced in critical illness, have been shown to upregulate the expression and membrane localization of these transporters in different cell types [54–58]. Hence, cellular glucose overload may develop in tissues with insulin-independent glucose uptake, such as the central and the peripheral nervous system, as well as in the endothelial, hepatic and immune cells, the renal tubules and the gastrointestinal mucosa [59]. In contrast, tissues that predominantly rely on insulin-dependent glucose transport via GLUT-4, such as skeletal muscle and myocardium, may be relatively well protected against hyperglycemia-induced cellular glucose overload and toxicity.

This is consistent with the demonstration that prevention of hyperglycemia with insulin therapy protected both the ultrastructure and function of the mitochondrial compartment in hepatocytes from critically ill patients, whereas no obvious morphological or pronounced functional differences were detected in the skeletal muscle of those patients [60]. In view of the tissue-specific differences in glucose uptake mechanisms, these data suggest that prevention of glucose overload and toxicity, rather than a direct effect of the administered insulin, is responsible for the beneficial effect of tight glucose control on mitochondria [49, 60–62]. However, many of the proposed benefits of normoglycemic control in critical illness are difficult to separate from the direct effects of

insulin on several cell and organ systems. Therefore, a key study performed in a burn-injured rabbit model independently manipulated blood glucose and insulin levels [62]. Reduction of glucose levels, rather than high insulin levels, was responsible for improved liver, kidney and endothelial function, while both factors contributed to improved leukocyte and myocardial functions.

Improvement of Lipid Metabolism

Lipid metabolism in critically ill patients is strongly deranged with elevated levels of triglycerides together with very low levels of HDL and LDL cholesterol [63–65]. These disturbances were almost completely (hypertriglyceridemia) or partially reversed (HDL and LDL cholesterol) by insulin therapy. Multivariate logistic regression analysis revealed that improvement of the dyslipidemia with insulin therapy explained a significant part of the reduced mortality and organ failure in critically ill patients [50]. The important role of lipoproteins in transportation of lipid components (cholesterol, triglycerides, phospholipids, lipid-soluble vitamins) and scavenging of proinflammatory bacterial endotoxin may have contributed to the improved outcome [66].

Anabolic Effect

Critical illness uniformly goes in line with a hypercatabolic state characterized by a profound protein breakdown despite adequate enteral or parenteral nutrition. Intensive insulin therapy might attenuate this catabolic syndrome of prolonged critical illness, as insulin has been shown to exert anabolic actions. Intensive insulin treatment indeed resulted in elevated total protein content in the skeletal muscle of critically ill patients and prevented weight loss in a rabbit model of prolonged critical illness [60, 67].

Nonmetabolic Effects

It has been shown that intensive insulin therapy prevents excessive inflammation, as illustrated by the lower levels of C-reactive protein and mannose-binding lectin [68]. Insulin therapy also attenuated the C-reactive protein response in an experimental rabbit model of prolonged critical illness induced by a third-degree burn injury. Monocytes from these critically ill rabbits showed an increased phagocytosis capacity and increased ability to generate an oxidative burst when blood glucose levels were kept normal [67]. In the same model, when blood glucose and plasma insulin levels were independently manipulated, leukocyte dysfunction was again only present in hyperglycemic rabbits, but could in part be rescued

by insulin [62]. Hyperglycemia can lead to glycosylation of immunoglobulins (which causes their inactivation), hence contributing to the risk of infection. High glucose levels also negatively affect polymorphonuclear neutrophil function and intracellular bactericidal and opsonic activity. These data indicate that prevention of hyperglycemia might indeed be a crucial factor contributing to the anti-inflammatory effects of intensive insulin therapy [69–71].

Prevention of endothelial dysfunction also contributed to the protective effects of insulin therapy in critical illness. This effect was in part mediated by the suppression of adhesion molecules and of inducible nitric oxide (NO) synthase (an enzyme that otherwise can cause excessive release of NO), and by the reduction of circulating levels of asymmetric dimethylarginine which inhibits the constitutive enzyme endothelial NO synthase, which normally is responsible for the necessary production of low amounts of endothelial NO [72, 73]. In critically ill rabbits, endothelial dysfunction (evaluated in isolated aortic rings) was prevented by maintaining normoglycemia, independent of insulin levels [62].

Intensive insulin therapy also attenuated the cortisol response to critical illness, without involvement of altered cortisol-binding activity [74].

Conclusions

Hyperglycemia in critically ill patients has been associated with increased mortality and morbidity. Evidence for a causal relationship has been provided by two large randomized controlled studies on maintenance of strict

normoglycemia with intensive insulin therapy, which improved survival and morbidity. Although these beneficial effects have been confirmed in observational implementation studies, criticism has been raised with regard to the Leuven studies. These issues have been briefly discussed in this review and systematically addressed in a recent review [75]. A major concern relates to the increased incidence of hypoglycemia with this therapy, for which it is unclear at this point whether it is truly harmful in the ICU setting. While waiting for the results of the NICE-SUGAR trial, the only study that is currently ongoing that is designed with sufficient statistical power to assess the impact of strict blood glucose control with intensive insulin therapy on survival, the current evidence favors the control of blood glucose levels below 110 mg/dl. Evidently, clear guidelines are needed as well as adequate education and training of the medical and nursing staff to safely implement strict blood glucose control, with optimal control of glucose levels and avoiding hypoglycemia. The Leuven studies showed that many lives were saved with this intervention, despite an elevated incidence of hypoglycemia. Studies on the underlying mechanisms revealed that prevention of glucose toxicity by strict glycemic control, but also other metabolic and non-metabolic effects of insulin, contribute to these clinical benefits.

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