

Glucose dysmetabolism and prognosis in critical illness

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Abstract Acute hyperglycemia frequently present in stress conditions, has long been generally accepted as normal, and not thought to be a cause for concern since a moderate hyperglycemia in critically ill adult patients has been thought to be beneficial during the “fight or flight” response to ensure a supply of glucose as a source of energy to organs that do not require insulin for glucose uptake (i.e., the brain and the immune system). However, an increasing body of evidence associates the upon-admission degree and duration of hyperglycemia during critical illness with an adverse outcome. Hyperglycemia should be regarded as a part of the systemic and complex metabolic derangements observed in critical illness in response to stress and inflammation, which can lead, independent of initial disease, to multiorgan dysfunction and death. A tight glycemetic control should be constantly pursued and achieved by insulin infusion bearing in mind that the therapeutic target is fighting the systemic inflammatory response and not merely the glucose plasma levels.

Keywords Hyperglycemia · Critical illness · Insulin resistance

Introduction

During the past decades, the evolution of critical care medicine has fostered a tremendous increase in the immediate survival of acutely ill patients who frequently enter a “chronic phase” of critical illness during which they are still dependent on vital organ support for quite a long period. In these patients, mortality remains high, with a 20% risk of death, mostly due to non-resolving multiple organ failure, regardless of the initial disease. In this phase, continuing hypercatabolism results in profound erosion of lean body mass despite artificial feeding and relative preservation of adipose tissue. Among other metabolic and endocrine abnormalities, these patients usually develop hyperglycemia, reflecting insulin resistance and accelerated glucose production, known as stress diabetes or the diabetes of injury [1, 2].

Acute hyperglycemia, frequently present in stress conditions [3, 4], has long been generally accepted as non-problematic, since a moderate hyperglycemia in critically ill adult patients has been thought to be beneficial during the “fight or flight” response to ensure the supply of glucose as a source of energy to organs that do not require insulin for glucose uptake (i.e. the brain and the immune system). However, an increasing body of evidence associates the upon-admission degree of hyperglycemia and the duration of hyperglycemia during critical illness with an adverse outcome. The important issue is whether hyperglycemia is just related to disease severity or is an independent risk factor that contributes to morbidity and mortality in critically ill adult patients [5].

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Glucose metabolism and critically illness

In physiological conditions, despite large timely fluctuations in supply and demand, plasma glucose levels are normally controlled within a narrow range between 80 and 125 mg/dl in a fasting state. Interestingly, 80% of systemic glucose utilization occurs by non-insulin-mediated glucose uptake under basal conditions, mainly by the central nervous system [6]. Glucose transport into cells occurs as facilitated diffusion using one of the five glucose transported (GLUT) channel proteins (GLUT1-mediated insulin independent transport mostly in basal conditions; GLUT4 specifically and reversibly up regulated by insulin). During moderate hyperglycemia, cells usually respond with a removal of GLUT transport molecules to protect themselves from glucose overload [7].

In the critically ill patient, the classic endocrine reaction to a stressful challenge consists of the activation of the sympathoadrenal and the hypothalamopituitary-adrenal axis, leading to increased plasma levels of catecholamines and glucocorticoids [1], and the degree of systemic response to stress correlates with the intensity of the challenge (Table 1).

Stress, imposed by any type of acute illness, leads to the development of insulin resistance, glucose intolerance and hyperglycemia [8] (Fig. 1). In the acute phase of critical illness, despite high plasma glucose levels and abundantly released insulin, hepatic glucose production is upregulated probably due to elevated levels of cytokines, growth hormone, glucagons and cortisol [2, 9]. Hepatic glycogenolysis is further enhanced by catecholamines that also inhibit glycogen-neogenesis [10]. Moreover, glucose uptake mechanisms are also affected in the critically ill and

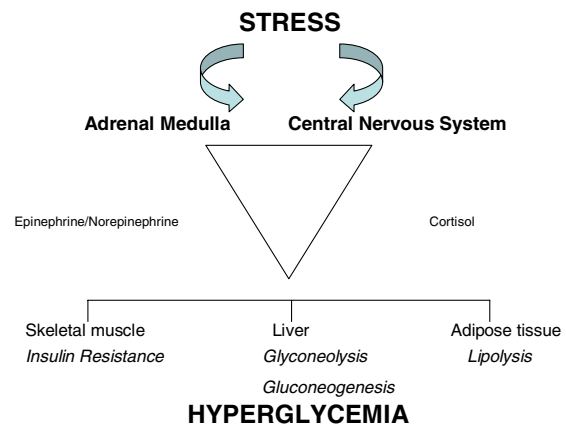


Fig. 1 The relationship between stress and hyperglycemia in the critically ill

contribute to hyperglycemia. Exercise-stimulated glucose uptake in skeletal muscle totally disappears because of immobilization [11]. Glucose uptake in heart, skeletal muscle, and adipose tissue is compromised because of impaired insulin-stimulated glucose uptake by the glucose transporter 4 (GLUT-4) and impaired glycogen synthetase [8]. Nevertheless, it has been observed that the total body glucose uptake is massively increased, but is accounted for by tissues that do not depend on insulin for glucose uptake such as brain and blood cells [1]. The higher levels of insulin, the impaired peripheral glucose uptake and the elevated hepatic glucose production reflect the development of an insulin resistance during critical illness.

Interestingly, in critically ill patients, hyperglycemia seems more acutely toxic than in healthy individuals (in whom cells can protect themselves by down-regulating glucose transporters [7]). There are two possible explanations, not mutually exclusive, for this phenomenon [12]. The first is the accentuated cellular glucose overload, and the second is the more pronounced toxic side effects of glycolysis and oxidative phosphorylation.

Cellular glucose overload

The central and peripheral nervous system, hepatocytes, endothelial, epithelial, and immune cells take up glucose independently of insulin. Three glucose transporters, GLUT-1, GLUT-2, and GLUT-3, facilitate insulin-independent glucose transport in these tissues. In physiological conditions, hyperglycemia induces a down-regulation in GLUT-1 transporters, thus protecting cells against glucose overload. Cytokines, growth factors and hypoxia all increased in critical illness have been shown to up-regulate expression of the glucose transporters (GLUT-1, GLUT2 and GLUT3), thus overriding the physiological down-regulatory protective response against hyperglycemia in several cellular types (hepatocytes, gastro-intestinal

Table 1 Main mechanisms of stress hyperglycemia and contributing hormones/factors

Mechanisms	Hormones/factors
Increased glycogenolysis	Glucagon Epinephrine
Increased gluconeogenesis	Glucagon Epinephrine/norepinephrine Corticosteroids Growth Hormone
Increased peripheral insulin resistance	
Skeletal muscle	Epinephrine/growth hormone/ epinephrine/TNF
Liver	TNF
Increased lipolysis	Epinephrine/norepinephrine Glucocorticoids Growth Hormone

mucosal cells, pancreatic beta-1 cells, renal tubular cells, endothelial cells, immune cells and neurons, all insulin independent for glucose uptake) [13]. Hence, particularly in critical illness, characterized by high circulating levels of all these regulators, all organ systems that take up glucose passively may theoretically be at high risk for direct glucose toxicity. In contrast, skeletal muscle and the myocardium, which normally take up glucose predominantly via the insulin-dependent GLUT-4 transporter, may be relatively protected against toxic effects of circulating glucose.

Increased oxidative phosphorylation in the critically ill

Vulnerability to glucose toxicity may be also due to increased generation of or deficient scavenging systems for radical oxygen species (ROS) produced by activated glycolysis and oxidative phosphorylation [14]. In physiological conditions, glucose in the cytosol undergoes glycolysis, and its metabolite pyruvate is further transformed into acetyl-CoA, after which, in the presence of O₂, oxidative phosphorylation generates ATP. Along with the generation of ATP by the mitochondrial respiratory chain complexes I–V, a small amount of superoxide is concomitantly produced. In physiological conditions, 2–5% of O₂ used in the mitochondria is metabolized into superoxide, which is subsequently detoxified by manganese superoxide dismutase (MnSOD). When more glucose enters the cell and more pyruvate is being used for oxidative phosphorylation, more superoxide will be generated [13]. Superoxide interacts with NO to form peroxynitrite, which nitrates several protein substrates such as mitochondrial complexes I and IV and MnSOD. During critical illness, hypoxia-reperfusion aggravates superoxide production and when, in this setting, cells are also overloaded with glucose, high levels of superoxide (together with nitric oxide metabolites) contribute to mitochondrial dysfunction (by inhibiting the glycolytic enzyme GAPDH and mitochondrial complexes I and IV). Liver biopsies reveal profound ultrastructural abnormalities in hepatocytic mitochondria of patients with moderate hyperglycemia in whom conventional insulin therapy is randomly administered, while no abnormalities are found in patients submitted to intensive insulin therapy [15]. The higher activity of respiratory chain complex I and complex IV can be considered the functional correlate of the prevention or reversal of these morphological abnormalities in hepatocytic mitochondria. Conversely, no major ultrastructural abnormalities are found in the mitochondria of skeletal muscle, thus suggesting that in this tissue, insulin therapy is not able to affect the respiratory chain activity. This phenomenon strongly suggests a direct effect of glucose control, rather than of insulin. In those tissues (such as immune and

endothelial cells, the central and peripheral nervous system) where glucose enters passively, reduction in plasma glucose levels would probably lead to prevention of hyperglycemia-induced mitochondrial dysfunction, thus explaining some of the protective effects of insulin therapy in critically ill patients. In fact, in the Leuven study [16], it is observed that maintaining normoglycemia with insulin is associated with a reduced incidence of severe nosocomial infections and lethal sepsis. Protection of the peripheral nervous system is evidenced by prevention of the development of critical illness polyneuropathy, which results in a shorter duration of mechanical ventilation and intensive care stay, while the observed reduced incidence of seizures [17] can be related to a more efficacious protection of the central nervous system.

At the cellular level, severe hyperglycemia has been found to induce repeated and acute changes in cellular metabolism and in the structure of macromolecules [14, 18]. In the presence of high glucose concentrations, several steps of the glycolytic pathways can induce the release of toxic derivatives, including polyols derived from glucose, hexosamines from fructose-6-phosphate, advanced glycation products, and activators of the protein kinase C pathway from glyceraldehyde-3-phosphate.

Prevalence and prognostic value of hyperglycemia

A correlation between hyperglycemia and mortality has been described in varying situations [19], even though different authors use different thresholds to define hyperglycemia.

Among patients admitted to a general hospital [20], hyperglycemia (defined as fasting blood glucose above 7 mmol/l to >140 mg/dl) is observed in 38%. Among the patients with newly discovered hyperglycemia, 16% die during hospital stay, as compared with only 1.7% of patients with normoglycemia ($P < 0.001$). Patients with new onset hyperglycemia are more often admitted to the ICU (29 vs. 19%) and have a longer hospital stay. In this investigation, known diabetic patients show a better prognosis than newly hyperglycemic patients.

In medical ICU patients [21] hyperglycemia is present in 23% of patients, while it is detectable in 86% of thoraco-surgical ICU patients [16]; most of them (96%) become hyperglycemic during their ICU stay.

Hyperglycemia is a risk factor for increased morbidity and mortality in critically ill surgical patients [22] but not in medical ones, though the number of medical patients enrolled in this study was small, and thus no firm conclusions can be drawn. In different ICU populations, data on the association between hyperglycemia and in-hospital mortality are controversial.

In a retrospective study [23] performed in a mixed ICU population, even a modest degree of hyperglycemia is associated with an increased in-hospital mortality, whereas in another retrospective study [5] hyperglycemia is not an independent risk factor for mortality in a multivariate model.

Whitcomb et al. [24] assess, in a retrospective cohort study, the generalizability of the association between hyperglycemia and in-hospital mortality in different intensive care unit types adjusting for illness severity and diabetic history. Admission blood glucose is used to classify patients as hyperglycemic (>200 mg/dL) or normoglycemic (60–200 mg/dL). The adjusted odds ratios for death comparing all patients with hyperglycemia to all those without are 0.81 (95% confidence interval, 0.37, 1.77) and 1.76 (95% confidence interval, 1.23, 2.53) for those with and without a diabetic history, respectively. A higher mortality is seen in hyperglycemic patients without a diabetic history in the cardiothoracic, (adjusted odds ratio, 2.84 [1.21, 6.63]), cardiac (adjusted odds ratio, 2.64 [1.14, 6.10]), and neurosurgical units (adjusted odds ratio, 2.96 [1.51, 5.77]), but not in the medical or surgical intensive care units, or in patients with a diabetic history. The authors conclude that the association between hyperglycemia on intensive care unit admission and in-hospital mortality is not uniform in the study population, and that hyperglycemia is an independent risk factor only in patients without a diabetic history in the cardiac, cardiothoracic, and neurosurgical intensive care units. Similarly Wahab et al. [25] document a two-fold increase in odds ratio for mortality in hyperglycemic non-diabetic patients, which is higher compared to the risk observed in diabetic patients. The reason that critically ill patients with a history of diabetes may not have the same degree of hyperglycemia-associated mortality as non-diabetic patients is not clear. It can be hypothesized that patients with a history of diabetes are more likely to receive intensive insulin treatment during their stay. In a recent paper by Giannazzo et al. [26] (and in the Editorial by Ban et al. [27]), in a retrospective study performed in patients admitted to the ED with a diagnosis of severe sepsis or septic shock, some therapy with insulin is the only variable related to a lower risk of death and, at univariate analysis, a history of diabetes predicts a favorable outcome. This phenomenon may be related to the fact that diabetics are treated earlier and much more aggressively since they are easily recognized as being at a higher risk of sepsis. Diabetic patients represent a unique patient population at higher risk for complications. Myocardial infarction is an uncommon but well recognized precipitant of diabetic ketoacidosis (DKA) accounting for 1% of cases. Myocardial infarction, and congestive cardiac failure account for 28% of deaths in DKA [28]. In a recent investigation [29], it is observed that

elevated troponin I in diabetic patients admitted with DKA identifies, though in the absence of clear acute coronary syndrome, a group at very high risk for future cardiac events and mortality. The triad of uncontrolled hyperglycemia, metabolic acidosis and increased total body ketone concentration characterizing DKA result from the combination of absolute or relative insulin deficiency and increased levels of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). All these factors taken together can contribute to the development of myocardial ischemia together with fluid shift, tachycardia, and increased sympathetic tone.

In patients with acute myocardial infarction (AMI) [30], mild or moderate impaired glucose levels (5–8 mmol/l to 100–160 mg/dl) are observed in 65% of patients while previously known diabetes is present in 15%. This investigation, performed in an unselected population of AMI patients, documents that admission glucose level is independently correlated with 1-year mortality, thus underlying the prognostic importance of impaired glucose in these patients. In a meta-analysis of 1,856 AMI patients [31], hyperglycemia is associated with an increased risk of in-hospital mortality in patients with and without diabetes; the risk of congestive heart failure or cardiogenic shock is increased in patients without diabetes. In a retrospective study with prospective follow-up performed in 846 AMI patients [32], the admission blood glucose level after AMI is confirmed as an independent predictor of long-term mortality in patients with and without known diabetes. The AMI patients with unknown diabetes and admission glucose levels of 200 mg/dL or more show mortality rates comparable to those with established diabetes. In 779 consecutive AMI patients from the Myocardial Infarction Registry in Estonia [33] hyperglycemia on admission, independent of a history of diabetes, represents an independent risk factor for 180-day mortality; non-diabetic hyperglycemic patients experience the worst outcome. Aaronson et al. [34] prospectively studied the relationship between fasting glucose level and long-term mortality in AMI patients, and find a graded independent association between glucose levels at admission and long-term mortality in non-diabetic patients. Both admission and fasting glucose levels provide incremental prognostic information with regard to long-term mortality when added to the GRACE risk score. However, fasting glucose provides greater incremental prognostic information than admission glucose. Furthermore, fasting glucose remains an independent predictor of long-term mortality after adjustment for left ventricular ejection fraction. Recently also in patients with acute coronary syndrome [35], an elevated glucose level on admission is a significant independent predictor of in-hospital mortality, and is even more important in patients who do not have known diabetes.

In a retrospective study in patients with an established cerebrovascular accident (CVA) [36] admitting hyperglycemia is common (about 40%), and is associated with increased short- and long-term mortality and with increased inpatient charges. In CVA patients without known diabetes but with an elevated blood glucose (>6.1 mmol/l to >122 mg/dl) [37], the risk of dying within 30 days is threefold higher than in the normoglycemic patients.

In trauma patients [38] even a mild hyperglycemia (>7.5 mmol/l to >150 mg/dl) is an independent predictor for mortality, postoperative infection and hospital and ICU length of stay. The relationship between hyperglycemia and mortality in these patients is more pronounced than in elective surgical patients [38]. It has been described that in trauma patients the elevated blood sugar, in the early phase, results from glycogen mobilization, while hyperglycemia in the late phase (4–5 days after injury) develops if organ failure or infectious complications ensue. Patients with hyperglycemia on admission have higher mortality rates, whereas blood glucose levels at 24 h do not correlated with outcome, particularly if the patient is adequately resuscitated with a normal lactate level [39]. As far as therapy is concerned, despite the increased use of insulin drips and the higher number of glucose checks after adopting a stricter insulin treatment protocol, ICU outcomes remained unchanged [40]. In an experimental model of activated macrophages [41], insulin does not prove to have direct anti-inflammatory properties.

On the basis of available literature data, the incidence of admission hyperglycemia in critically ill patients is quite high, and in the vast majority of the studies, inpatient hyperglycemia is associated with a lower survival rate [19, 42]. Many of the currently available studies are limited because they do not adequately control for severity of illness, they focus only on specific subsets of patients, or they define hyperglycemia by admission glucose only. However, these observational studies have been informative in areas where randomized trials are difficult or impractical.

Insulin and the critically ill

Benefits of insulin therapy in critically illness

The Leuven Study [16], a prospective, randomized, controlled investigation of a large group of patients (the majority of whom did not previously have diabetes) shows that titrating insulin infusion during intensive care to strict normoglycemia (below 110 mg/dl) strikingly reduces mortality (43% reduction) when compared with conventional insulin treatment. Besides, intensive insulin therapy largely prevents critical associated complications; the

incidence of critical illness polyneuropathy is reduced by 44%, the development of bloodstream infections by 46% and acute renal failure requiring dialysis or hemofiltration by 41%. Patients are also less dependent on mechanical ventilation. The clinical benefits of this regimen are also observed in most diagnostic subgroups such as patients with isolated brain injury [43].

The clinical benefits of insulin therapy are also observed in a heterogeneous medical and surgical population in a non-randomized setting [16, 44]. In a prospective, randomized, controlled study of adult medical patients admitted to ICU [3], it is clearly demonstrated that insulin therapy reduces morbidity and mortality of patients treated at least a few days in the ICU. A higher number of deaths are documented in the group of short-stay patients on intensive insulin therapy, and although this difference is not statistically significant and likely explained by selection bias, it is of concern to the practicing clinician.

Pooling the two data sets of randomized controlled trials [16, 45] generates equal-sized samples of long-stay and short-stay medical/surgical ICU patients. Intensive insulin therapy significantly reduces morbidity and mortality in mixed medical/surgical ICU patients in an intention-to-treat analysis. This effect is increased when the therapy is continued for at least 3 days, independent of parenteral glucose load, and without causing harm to patients treated for <3 days. Patients with a prior history of diabetes do not appear to show benefit, probably because in these patients a rapid normalization of blood glucose levels can be deleterious especially if their blood glucose levels before ICU admission are elevated. [45].

Other studies on insulin intensive therapy in different patients' subsets

In patients with AMI, the infusion of glucose together with insulin and potassium (GIK) is associated with a reduction in early mortality and morbidity, thus yielding promising results [46]. However, recently two large, randomized trials on GIK therapy in AMI patients (CREATEECLA [Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation: Estudios Cardiológicas Latin America]) and in AMI patients with diabetes and myocardial infarction (DIGAMI-2, [second Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction study]) do not show clinical benefits of this treatment [46, 47]. In the CREATE-ECLA study, the patients who received GIK and those who did not show a comparable mortality and incidence of cardiac arrest, cardiogenic shock, and reinfarction [47]. However, no simultaneous glucose control was performed, and GIK therapy was associated with an increase in glucose levels even compared with the usual care. The DIGAMI-2 trial

[48] was set up to investigate whether the clinical benefit of the first DIGAMI study [49–51] was mediated by an acute effect of GIK and that of blood glucose control during the months after the infarction. This study observes no significant effect on morbidity and mortality, assessed by the occurrence of non-fatal reinfarctions and strokes. However, the target of normal glucose levels assigned to one of the groups was not reached, thus excluding an acute effect of GIK in the absence of blood glucose control. Therefore, no conclusion can be drawn with respect to the effect of blood glucose control because of unintended protocol violation.

Similarly, GIK infusion for 24 hrs following *acute stroke* does not realize a significant reduction in glycemia or mortality, as reported in the Glucose–Insulin in Stroke Trial (GIST) [52]. Recently [53] in a multicenter, two-by-two factorial trial, patients with severe sepsis were randomly assigned to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5), or modified Ringer’s lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were coprimary end points. The trial was stopped early for safety reasons. Among 537 patients who could be evaluated, the mean morning blood glucose level is lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol per liter]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol per liter], $P < 0.001$). However, at 28 days, there is no significant difference between the two groups in the rate of death or the mean score for organ failure. The rate of severe hypoglycemia (glucose level, ≤ 40 mg per deciliter [2.2 mmol per liter]) is higher in the intensive-therapy group than in the conventional-therapy group (17.0 vs. 4.1%, $P < 0.001$), as is the rate of serious adverse events (10.9 vs. 5.2%, $P = 0.01$). The HES therapy is associated with higher rates of acute renal failure and renal-replacement therapy than is Ringer’s lactate.

In “real-life” intensive care of a heterogeneous critically ill medical/surgical patient population, the clinical benefits of implementing a tight glucose management protocol, by comparison with historical controls as a reference are confirmed in an observational study [44]. Intravenous insulin was administered only if glucose levels exceeded 200 mg/dL on two successive measurements and aimed to lower glycemia to 140 mg/dL, (which is less strict than in the Leuven studies). When compared to a historical control group, the implementation of the glucose control protocol results in a significant reduction in hospital mortality (from 20.9 to 14.8%) as well as length of ICU stay decrease. There is a reduction in the incidence of new renal failure, need for red blood cell transfusion, and costs [54], but no significant difference in the occurrence of severe infections. In a prospective, randomized, controlled clinical trial

[55] conducted in glucose-intolerant surgical ICU patients without diabetes, a regimen with strict insulin therapy (target glucose range, 80–120 mg/dL) induces a significant reduction in the incidence of total nosocomial infections, including the sites of intravascular devices, bloodstream, intravascular device-related bloodstream, and surgical site infections, although the therapy is associated with a higher incidence of hypoglycemia.

Discrepancies between study results can be related to several factors: differences in patient selection criteria, in statistical power and in glucose target. Therefore, the tight glycemic control reached by the intensive insulin therapy reported in the Leuven studies cannot be merely extended to all critically ill patient subgroups without bearing in mind that available literature especially for specific subgroups, is scarce and rather controversial. An accurate knowledge of previous reports and glucose metabolisms in different critical settings can help intensivists who daily face the management of glucose control in their patients.

Mechanisms explaining the acute life-saving effects of intensive insulin therapy in the ICU

Since critically ill patients suffer from hepatic and skeletal muscle insulin resistance, the mechanism by which insulin lowers blood glucose in critically ill patients is not obvious. Analyses of liver and skeletal muscle biopsies, obtained immediately after death from non-survivors in the Leuven study [16] suggest that in the critically ill patient, insulin lowers blood glucose predominantly through increased skeletal muscle glucose uptake [56]. In the critically ill patient, adipose tissue and skeletal muscle remain relatively responsive to insulin, whereas the liver is much more resistant. The β cells appear unable to compensate fully for hyperglycemia.

Other metabolic effects of insulin in the critically ill

Improvement of dyslipidemia

Insulin exerts other metabolic effects besides the control of blood glucose. Critically ill patients most characteristically show elevated triglycerides and very low levels of high density lipoprotein and low-density lipoprotein cholesterol. On the other hand, the numbers of circulating small, dense LDL particles, which presumably are more proatherogenic than the medium and large LDL particles [57], are increased [58]. Interestingly, intensive insulin therapy can in part restore this dyslipidemia, with almost complete reversal of the hypertriglyceridemia and a substantial increase in, but not normalization of the serum levels of HDL and LDL [49]. A contribution of insulin therapy to improved outcome can also be explained given the

important role of triglycerides in energy provision and of lipoproteins in transportation of lipid components and endotoxin scavenging [59–61]. In the Leuven study multivariate logistic regression analysis demonstrates that the improvement of dyslipidemia with insulin therapy explains a significant part of the beneficial effect on mortality and organ failure. Surprisingly, its effects surpass those of glycemic control and insulin dose [56].

Anabolic effects

During critical illness, once a caloric deficit of 25–30 kcal/kg/d over 1 week is reached, mortality rates double [62]. Hyperglycemia per se seems to be associated with protein catabolism, as inferred by the increased rate of muscle wasting [63]. Another possible mechanism by which insulin improves outcomes is by blunting the catabolic response to stress and inflammation. In physiological conditions, the binding of insulin to its receptor suppresses proteolysis and activates protein synthesis. In animals, insulin therapy has been demonstrated to prevent weight loss [64], whereas in humans, insulin therapy has been associated with an increase in the protein content of skeletal muscle [15]. The exact mechanism explaining the anabolic effect of insulin therapy is still unknown since multiple anabolic factors, including growth hormone secretion, are affected by intensive insulin therapy [56]. It still unclear whether hyperglycemia and insulin therapy or the resolution of the underlying systemic inflammatory response is responsible for the reversal of catabolism; whatever the case, improved outcomes are noted (Fig. 2).

Other non-metabolic effects of insulin in the critically ill

Anti-inflammatory effects

Critical illness also resembles diabetes mellitus in the activation of the inflammatory cascade, although the inflammation, as reflected by a high circulating level of C-reactive protein (CRP), in the critically ill is several times more pronounced than in diabetic patients.

Hyperglycemia per se induces a pro-inflammatory state, which includes both cellular and oxidative stress. At the cellular level, glucose is known to increase pro-inflammatory transcription factors (such as intranuclear NF κ B binding, activator protein-1 and early growth response-1) that are suppressed by insulin. I Nevertheless, hyperglycemia can produce cellular inflammation at low levels of plasma glucose. As little as a 75-g glucose load given orally to normal subjects results in profound oxidative stress and inflammatory changes at the cellular and molecular levels [65].

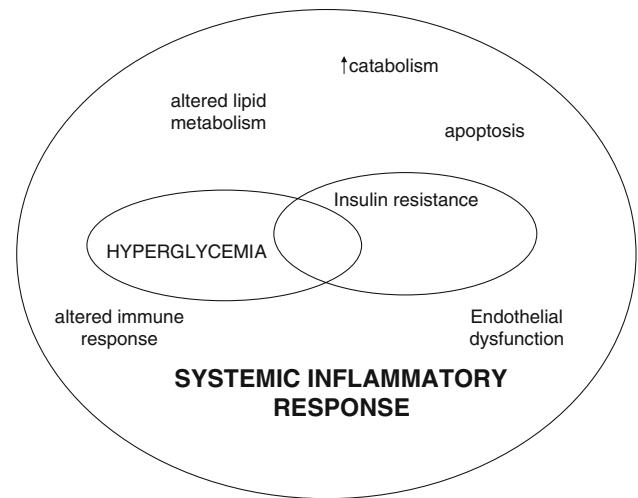


Fig. 2 Metabolic derangements and systemic inflammatory response in the critically ill

According to some authors, the anti-inflammatory properties of insulin account for the beneficial effects of insulin therapy, regardless of the degree of glucose control [16, 56, 66]. In critically ill patients, intensive insulin therapy induces a significant reduction in CRP (complement reactive protein) level, as confirmed in animal models of critical illness [64]. However, it has not so far been elucidated whether insulin exerts its anti-inflammatory effects directly at the level of NF κ B pathways or by lowering glucose to subsequently decrease systemic inflammation. Whatever the mechanism, the effect is rapid (observed within 2 h), and potent, since the magnitude of 2 units/h of insulin is similar to the effects of 100 mg of hydrocortisone given intravenously [67].

Preventing endothelial dysfunction and hypercoagulation

In critically ill patients [68] intensive insulin therapy reduces the circulating levels of the adhesion molecules ICAM-1 and E-selectin, independent of its effect on infection prevention. E-selectin is produced by endothelial cells, is rapidly inducible, and as such, reflects the state of the endothelium in disease. ICAM-1 is constitutively expressed at very low levels on the endothelium, and is highly inducible upon cell activation. It is also expressed by fibroblasts and hematopoietic cells. Small changes in the expression of the adhesion molecules at the endothelial cell level may go undetected in the circulation, but when differences in the amount of shedded adhesion molecules are found, this indicates a substantial change in the activity status of the endothelium. According to these authors, the lowering of ICAM-1 and E-selectin levels with intensive insulin therapy explains, at least in part, the reduced risk of developing organ failure and death with this intervention.

Anti-apoptotic effects

The literature so far available, describes only experimental models. It supports the hypothesis that insulin itself has direct cardioprotective effects during reperfusion, mainly via anti-apoptotic properties that are independent of glucose uptake [69–71]. The insulin signaling pathways involve include PI3K, Akt, and eNOS phosphorylation [69]. Whether such direct insulin-induced cell survival plays a role in mediating the observed protection of organ function in the critically ill remains unclear.

Glucose control or insulin therapy per se affects prognosis in critically ill patients

The Leuven study [16] performs a post hoc multivariate logistic regression that documents that both high insulin dosing and hyperglycemia independently predict ICU mortality, thus suggesting that the glucose-lowering effects are the key mechanism of action. Moreover, there is also a lower risk of death as blood glucose levels are lowered from 200 mg/dL to 150 mg/dL, and again to levels <110 mg/dL. Similarly in another large prospective trial [72] it is observed that control of glucose levels over absolute exogenous insulin levels accounts for the mortality improvement associated with intensive insulin therapy. These concepts are recently supported in an animal model of prolonged and critical illness (burn-injured, parentally fed rabbits) [73] The authors report that mortality is significantly lower in the two normoglycemic groups independent of insulin levels, and that maintaining normoglycemia, independent of insulin levels, prevents endothelial dysfunction as well as liver and kidney injury. Although the actions of intensive insulin therapy are clearly complex, and the exact mechanism(s) by which benefit occur is uncertain, both human and animal data strongly support glycemic control in the critical care unit by means of insulin therapy.

Conclusions

It has long been thought that hyperglycemia in the acute clinical setting may be beneficial, but recent evidence challenges this notion. In fact, several observational studies published over the last decade establish that hyperglycemia is a common abnormality in critically ill patients that is associated with increased morbidity and mortality, independent of pre-existing diabetes. Intervention studies that lower glucose with insulin demonstrate improved outcomes, suggesting that elevated glucose is a cause rather than just a marker of illness. Evidence suggests that hyperglycemia is a potentially correctable abnormality that

has deleterious effects in critically ill individuals. In other words, a simple metabolic intervention, that is maintaining normoglycemia with insulin, can lead to an improvement in survival and reduced morbidity of critically ill patients.

Hyperglycemia should be regarded as a part of the systemic and complex metabolic derangements observed in critical illness in response to stress and inflammation that can lead, independent of initial disease, to multiorgan dysfunction and death. In critically ill patients, a tight glycemic control should be constantly pursued and achieved by insulin infusion remembering that the therapeutic target is fighting the systemic inflammatory response and not merely the glucose plasma levels.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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