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REVIEW

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Stress-hyperglycemia, insulin and immunomodulation in sepsis

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Abstract Stress-hyperglycemia and insulin resistance are exceedingly common in critically ill patients, particularly those with sepsis. Multiple pathogenetic mechanisms are responsible for this metabolic syndrome; however, increased release of pro-inflammatory mediators and counter-regulatory hormones may play a pivotal role. Recent data suggests that hyperglycemia may potentiate the pro-inflammatory response while insulin has the opposite effect. Furthermore, emerging evidence suggests that tight glycemic control will improve the outcome of critically ill patients. This paper reviews the pathophysiology of stress hyperglycemia in the critically ill septic patient and outlines a treatment strategy for the management of this disorder.

Keywords Insulin · Glucose · Sepsis · Sepsis syndrome · Critical illness · Insulin resistance · Hyperglycemia

Introduction

In recent decades the reported incidence of sepsis has increased dramatically, largely due to the advancing age of the population, an increased number of invasive procedures being performed and immunosuppressive therapy [1]. In the United States, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal [2]. Despite the use of antimicrobial agents and advanced life-support care, the case fatality rate for patients with sepsis has remained between 30 and 40% over the past three decades [2, 3].

When the body is challenged by foreign microbial agents homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without damaging the host. This involves the activation of pro- and anti-inflammatory pathways which are tightly controlled and regulated [4]. In most infected persons, the body is able to achieve a balance between pro-inflammatory and anti-inflammatory mediators and homeostasis is restored. In some patients, however, this balance is upset with an excessive pro-inflammatory response resulting in the systemic inflammatory response syndrome (SIRS), multisystem organ dysfunction, and ultimately death [4, 5, 6, 7]. Attempts at down-regulating the pro-inflammatory response with novel agents directed at specific pro-inflammatory mediators has uniformly met with failure [4, 8, 9, 10]. Recent provocative data suggests that tight glycemic control with insulin may the restore the balance between pro-inflammatory and anti-inflammatory mediators and improve the outcome of critically ill patients [11, 12].

In this article we review the physiology of stress hyperglycemia and the immune-modulatory role of insulin in critically ill patients. The reader should be cautioned that many of the studies quoted in our review were performed in non-critically ill patients, many of whom were diabetic. While it is likely that the pathogenetic pathways are similar in both groups of patients, many of these postulates remain unproven in the critical care setting.

Endocrinology of stress

Stress associated with critical illness is characterized by activation of the hypothalamic–pituitary–adrenal (HPA) axis with the release of cortisol from the adrenal gland [13]. Activation of the HPA axis with the release of cortisol is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis.

In addition to increased cortisol secretion the stress response is characterized by a marked increase in the release of norepinephrine and epinephrine as well as glucagon and growth hormone [14, 15, 16]. Insulin levels are usually normal or decreased, despite peripheral insulin resistance [17, 18, 19]. It has been suggested that insulin release may be suppressed as the result of increased activation of the pancreatic alpha receptors [19]. In addition to causing insulin resistance, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) inhibit insulin release, an effect which appears to be concentration dependent [20]. The low to normal insulin levels together with insulin resistance in the presence of increased secretion of the counter-regulatory hormones results in stress hyperglycemia (see discussion below).

Glucose transporters and the mechanism of insulin action

Glucose is normally taken up across the cellular membranes by a system of carrier-mediated facilitated transport [21]. Five transporter isoforms exists. Three of the isoforms, GLUT 1, GLUT 2, and GLUT 4, are important for glucose uptake [21]. GLUT 1 can be found in many tissues and is responsible for basal uptake. It has a high affinity for glucose and it ensures transport even under the conditions of hypoglycemia. GLUT 2 mediates uptake and release of glucose by hepatocytes and regulation of glucose-stimulated insulin secretion in pancreas. The GLUT2 transporter ensures that the liver is freely permeable to glucose and that glucose transport is not rate-limiting for hepatic glucose uptake. GLUT 4 isoform is involved in glucose transport in tissues where uptake is mediated by insulin which includes skeletal muscle, cardiac muscle, and adipose tissue. Binding of insulin to cell-surface receptors results in autophosphorylation and activation of an intrinsic tyrosine kinase molecule of the insulin receptor (IR) b-subunit. Activated tyrosine kinase subsequently phosphorylates messenger molecular proteins known as insulin receptor substrates (IRS1 and IRS2). The IRS-1 associates with several proteins including the enzyme phosphatidylinositol (PI) 3-kinase. Physiologically insulin increases glucose uptake into the cell by causing translocation of GLUT 4 from intracellular compartments to the plasma membrane. The signaling enzyme molecule PI-3-kinase is essential for insulin stimulated GLUT 4 translocation [22]. PI-3-kinase also mediates many of the metabolic effects of insulin, including activation of glycogen synthase, protein synthesis, lipogenesis, and the regulation of various genes in insulin-responsive cells including inhibition of phosphoenol pyruvate carboxykinase (PEPCK), the key enzyme of gluconeogenesis.

Mechanisms of stress-induced hyperglycemia and insulin resistance in sepsis

The prevalence of stress hyperglycemia in sepsis and critical illness is difficult to establish due to limited data and variations in the definition of hyperglycemia. Stress hyperglycemia has been previously defined as a plasma glucose above 200 mg/dl [23]; however, in view of the results of the Leuven Intensive Insulin Therapy Trial (see below), stress hyperglycemia should be considered in any critically ill patient with a blood glucose in excess of 110 mg/dl [11]. In a study of septic non-diabetic ICU patients 75% had a baseline blood glucose level above 110 mg/dl [24]. In the Leuven Intensive Insulin Therapy Trial, 12% of patients had a baseline blood glucose above 200 mg/dl; however, 74.5% of patients had a baseline blood glucose above 110 mg/dl, with 97.5% having a recorded blood glucose level above 110 mg/dl sometime during their ICU stay [11].

Changes in whole-body glucose uptake and glucose oxidation in sepsis are complex and may depend on the severity of illness and the stage of the disease. Whole-body glucose uptake and glucose oxidation may be increased in the early stages of sepsis and endotoxemia [25, 26]. This may be the result of cytokine-induced increase in non-insulin mediated glucose uptake by tissues rich in mononuclear phagocytes, including the liver, spleen, ileum, and lung [27, 28]. Enhanced non-insulin mediated glucose uptake appears to result from an increase in the synthesis, concentration or activity of the GLUT1 transporter [29, 30]. With the development of insulin resistance (see below) glucose utilization and oxidation may decrease [25, 31, 32]. Exogenous insulin increases glucose utilization and oxidation; however, non-oxidative disposal (storage) remains impaired [25, 31, 32].

The metabolic milieu in which stress-induced hyperglycemia develops in the critically ill in the absence of pre-existing diabetes mellitus is complex. A combination of several factors, including the presence of excessive counter regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids, and cytokines such as IL-1, IL-6, and TNF-α combined with exogenous administration of catecholamines, dextrose, and nutritional support together with relative insulin deficiency, play an important role [23]. Increased gluconeogenesis combined with hepatic insulin resistance are the major factors

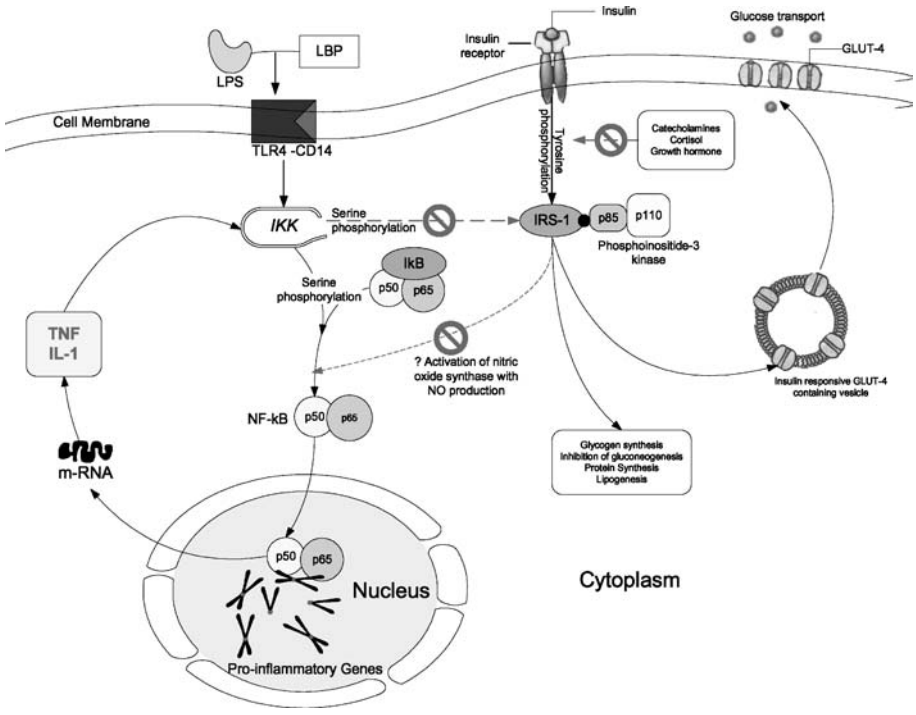

Fig. 1 Postulated interaction between the insulin signaling pathway and activation of the pro-inflammatory cascade in the pathogenesis of stress hyperglycemia of sepsis. *LPS* lipopolysaccharide, *LBP* lipopolysaccharide binding protein, *TLR4* Toll-like receptor 4, *IκB* inhibitor, *IKK* inhibitor κB kinase, *IRS-1*, insulin receptor substrate-1, *IL-1* interleukin-1, *TNF* tumor necrosis factor, *NF-kB* nuclear factor-kappa B

leading to hyperglycemia [33]. Recent human data suggests that hepatic insulin resistence (and PEPCK suppression) remains refractory to intensive insulin therapy [34]. Increased hepatic output of glucose may therefore be more important than peripheral insulin resistance in the genesis of stress hyperglycemia [35]. Gluconeogenic substrates released during stress include lactate, alanine, and glycerol with exogenous glucose failing to suppress gluconeogenesis [16, 36]. Glucagon is the primary hormonal mediator of gluconeogenesis, with septic patients having a significant increase in serum glucagon levels [16]. This effect is mediated by adrenergic stimulation by catecholamines and by cytokines [37]. In addition, cytokines such as TNF-α and IL-1 and catecholamines independently and synergistically promote hepatic glucose production [38, 39].

Sepsis is characterized by marked insulin resistance [19, 25, 31, 32, 40, 41]. The insulin resistance in sepsis is directly proportional to the severity of stress response [19]. During sepsis, insulin induced tyrosine phosphorylation of IRS-1 and subsequent activation of PI-3-kinase is impaired resulting in defective GLUT-4 receptor translocation, diminished glucose uptake, insulin resistance in skeletal muscle, and hepatic insulin resistance [22]. The mechanism whereby sepsis induces these alterations are unknown, but increased levels of TNF-α may play a key role. Aljada and colleagues have demonstrated that in endothelial cells TNF-α causes a reduction of tyrosine phosphorylation and expression of the insulin receptor [42]. TNF-α diminishes insulin-induced IRS-1 tyrosine phosphorylation in hepatocytes and adipocytes and impairs the activation of PI-3 kinase [43, 44, 45, 46]. These alterations of the early steps in insulin action are probably mediated by TNF-α induced IRS-1 serine phosphorylation [43, 46, 47, 48]. Upon serine phosphorylation, IRS1 proteins have a reduced ability to interact with the insulin receptor, to be tyrosine phosphorylated by the insulin receptor and to bind phosphatidylinositol-3 kinase [44, 45].

Recently, Gao and colleagues have demonstrated that activation of the inhibitor κB kinase (IKK) complex is associated with serine phosphorylation of IRS-1 [49]. The IKK is activated by endotoxin via Toll-like receptor 4 (LTR4) as well as by TNF-α and interleukin-1 (IL-1) [50, 51, 52]. The IKK is a serine kinase that controls the activation of nuclear factor-kappa B (NF-κB) a ubiquitous nuclear transcription factor closely associated with the activation of the genes for almost all of the pro-inflammatory mediators [53]. Before activation, NF-κB is bound to inhibitor κB (I κB). This association between I κB and NF-κB results in the cytosolic localiazation of NF-κB. The serine phosphorylation of I κB by the IKK complex results in the degradation of I κB followed by the nuclear translocation of NF κB. The serine phosphorylation of IRS-1 and I κB by IKK may partly explain the insulin resistance noted with activation of the pro-inflammatory cascade (see Fig. 1).

Catecholamines have also been shown to inhibit insulin binding, tyrosine kinase activity, and translocation of GLUT-4 either directly through a receptor or a post-

receptor mechanism [54, 55]. Blockade of α_2 adrenergic receptors has been demonstrated to reduce insulin resistance in septic rats [40]. Glucocorticoids impair insulin mediated glucose uptake in skeletal muscle, by down regulating various signaling proteins with resulting inhibition of translocation of GLUT-4 glucose transporter from its internal membrane stores to the plasma membrane [56]. Growth hormone inhibits the insulin pathway by reducing insulin receptors and impairing its activation through phosphorylation on tyrosine residues [57, 58].

Deleterious effects of hyperglycemia in the critically ill

To some extent the deleterious effects of hyperglycemia in the critically ill are similar to that of actual diabetes, although the time scale obviously differs [59]. Stress hyperglycemia but not pre-existing diabetes has been shown to be associated with a worse outcome following acute myocardial infarction and stroke [60, 61, 62, 63, 64, 65, 66]. The plasma glucose level on admission has been shown to be an independent predictor of prognosis after myocardial infarction [60, 61]. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg/dl improves outcome [62, 63, 64]. The presence of hyperglycemia following an ischemic or hemorrhagic stroke is associated with a two- to threefold increased mortality and significant impairment in functional recovery [65, 66].

Pro-inflammatory effects

Glucose has been shown to be a powerful pro-inflammatory mediator [67], and tight glucose control below 110 mg/dl with insulin has been shown to exert anti-inflammatory effects in the critically ill patient [68]. The oral administration of 75 g of glucose to healthy volunteers increases reactive oxygen species (ROS) generation by polymorphonuclear leukocytes and mononuclear cells [69]. Similarly, an oral glucose load has been demonstrated to increase plasma IL-8 levels [70]. Chettab and coworkers have demonstrated that hyperglycemia upregulates the IL-8 gene [71]. IL-8 is a potent neutrophil chemoattractant, playing an important role in inflammation [72, 73, 74]. Glucose induces an increase in intranuclear NF-κB, a fall in cytosolic I κB, and an increase in I κB kinase in vivo and in vitro which are pro-inflammatory [75, 76, 77]. Glucose also has been shown to exert pro-thrombotic effects and to increase oxidative stress due to increased lipid peroxidation [78, 79]. Glucose increases the expression and plasma concentration of matrix metalloproteinase-2 (MMP-2) and MMP-9, which aid in spread of inflammation [80]. Acute hyperglycemia reduces endothelial nitric oxide levels, causing abnormal vascular reactivity and organ perfusion [81].

Increased susceptibility to infection

In diabetic patients hyperglycemia has long been known to increase the susceptibility to infections [82]. In critically ill surgical and burn patients tight glycemic control has been demonstrated to reduce the risk of septic morbidity [11, 83, 84, 85]. The in vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycemic control [86, 87]. Rassias and colleagues demonstrated that tight glycemic control partially prevented the postoperative decrease in neutrophil phagocytic activity [88]. In addition, hyperglycemia has been demonstrated to decrease the oxidative burst of leukocytes [89, 90].

Immune-modulatory role of insulin in sepsis

Besides control of hyperglycemia, insulin has potent acute anti-inflammatory effects. In a group of obese subjects, Dandona and colleagues demonstrated that an infusion of insulin was associated with a significant fall of intranuclear NF-κB, and increase in IκB in mononuclear cells [91]. These changes were associated with a fall in the generation of reactive oxygen species and a fall in the serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1) [91]. In a similar experiment Aljada et al. demonstrated that insulin decreased expression of the pro-inflammatory transcription factor, early growth response-1 (EGR-1), and this was associated with a significant fall in plasma tissue factor (TF) and PAI-1 levels [92]; thus, while hyperglycemia has pro-thrombotic effects, insulin has anti-thrombotic and fibrinolytic effects by suppressing TF and PAI-1.

One mechanism underlying the anti-inflammatory effect of insulin may be through the release of nitric oxide (NO) from the endothelium. Insulin has been demonstrated to induce an increase in the expression NO synthase (NOS), the enzyme that generates NO [93]. The NO has been demonstrated to down-regulate the expression of endothelial cell adhesion molecules (ECAMs) as well as the pro-inflammatory cytokines [94, 95, 96, 97, 98]. While the anti-inflammatory effects of NO have not been fully delineated, it is thought that NO inhibits the activation of NF-κB. Several authors have demonstrated that NO *S*-nitrosylates a key thiol group in the DNA binding domain of NF-κB p50 and that this is associated with decreased gene transcription and synthesis of NF-κB [96, 99, 100].

NF-κB as a therapeutic target for tight glycemic control

NF-κB is a nuclear transcription factor involved in the regulation of over 150 genes related to inflammation, including TNF-α, IL-1, IL-6, IL-8, cyclooxygenase-2, and inducible nitric oxide synthase [53, 101]. Excessive activation of NF-κB has been identified as a marker of poor prognosis in sepsis [102, 103, 104]. Emerging data suggests that NF-κB may be a therapeutic target for the adjuvant treatment of sepsis [105, 106, 107, 108]. The data cited above suggests that tight glycemic control with insulin may decrease NF-κB activation. This hypothesis is supported by the Leuven Intensive Insulin Therapy Trial in which mannose-binding lectin (MBL) and C-reactive protein (CRP) levels were significantly suppressed by intensive insulin therapy [68].

Intensive insulin therapy in the critically ill

Van Den Berghe et al. in a prospective randomized controlled study involving 1548 patients demonstrated that intensive insulin therapy reduced mortality and morbidity among patients admitted to a surgical critical care unit (the Leuven Intensive Insulin Therapy Trial) [11, 12]. These authors compared an intensive insulin therapy regimen aimed to maintain blood glucose between 80 and 110 mg/dl with conventional treatment in which insulin infusion was only initiated when glucose level was greater than 215 mg/dl and maintenance of glucose between 180 and 200 mg/dl. At 12 months the mortality was 4.6% with the intensive insulin regimen compared with 8.0% in the control group. The benefit was most apparent in patients with greater than 5 days of stay in the intensive care unit. Intensive insulin therapy reduced bloodstream infections by 46%, acute renal failure by 41%, and critical illness poly-neuropathy by 44%. Using multivariate analysis the authors suggested that improved metabolic control, as reflected by normoglycemia, rather than the infused insulin dose per se, was responsible for the beneficial effects of intensive insulin therapy [12]; however, achieving normoglycemia and the administration of insulin are linked, and from the available evidence it appears likely that both factors played a key role in the improved outcome.

The outcome data from the Leuven Intensive Insulin Therapy Trial indicates that there is a dose response curve between the degree of glycemic control and hospital mortality [12] In the long stay patients (>5 days in the ICU) the cumulative hospital mortality was 15% in patients with a mean blood glucose less than 110 mg/dl, 25% in those with a blood glucose between 110 and 150 mg/dl, and 40% in those with a mean blood glucose of greater than 150 mg/dl. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg/dl improves outcome [62, 63, 64]. This data suggests that even "modest" glycemic control will have an impact on patient outcome. This is very important as in the "real world" it may be very difficult (if not somewhat risky) to attempt to maintain a blood glucose in the range of 80–110 mg/dl. This goal may only be achievable in ICUs with a high nursing-to-patient ratio and close physician supervision. On the other hand, the Leuven study showed that in order to improve morbidity by reducing the incidence of bacteremia, acute renal failure, critical illness polyneuropathy, and transfusion requirements, a blood glucose level of <110 mg/dl was required. Indeed, a blood glucose level of 110–150 mg/dl was not effective on these morbidity measures as compared with >150 mg/d [12]. It is also important to note that in the Leuven Intensive Insulin Therapy Trial all patients received between 200 and 300 g of intravenous glucose on the day of admission followed by parenteral or enteral (or both) nutrition started on the second ICU day. In this study tight early glycemic control was associated with the more rapid improvement of insulin resistance [12]. Based on the results of this study we recommend the initiation of parenteral glucose and enteral nutrition in all ICU patients on the day of ICU admission [109, 110, 111] and the initiation of an insulin infusion in patients with a blood glucose above 150 mg/dl (a threshold of 110 mg/dl may be appropriate in select ICUs). Subcutaneous insulin "sliding scales" are not recommended, at least during the first few days, until the patient's medical condition has stabilized, the blood glucose is well controlled, and the patient has achieved his/her nutritional goal.

Thiazolidinediones are a new class of drugs that are used in the treatment of type-II diabetes mellitus. These drugs reduce insulin resistence through its binding to peroxisome proliferator-activated receptors-λ (PPARλ). Ghanim and colleagues demonstrated that troglitazone caused a significant fall in cellular NF-κB with an increases in I κB in mononuclear cells of diabetic subjects [112]. The changes were associated with a parallel fall in serum levels of TNF-α, sICAM, MCP-1, and PAI-1. While one expects these effects to be useful in chronic situation, it is relevant that these anti-inflammatory were observed within 3–7 days [112, 113]. In an experimental model of acute myocardial infarction, even a single dose of rosiglitazone has been shown to reduce myocardial damage by 50% [114, 115]. Thiazolidinediones may therefore have a role in the metabolic management of patients with sepsis; however, clinical studies are required before these agents can be recommended.

Conclusion

Stress-hyperglycemia and insulin resistance are almost universal findings in patients with sepsis. Multiple pathogenetic mechanisms are responsible for this metabolic

syndrome; however, increased release of pro-inflammatory mediators and counter-regulatory hormones may play a pivotal role. Hyperglycemia per se is pro-inflammatory, whereas insulin has anti-inflammatory properties. Emerging evidence suggests that tight glycemic control with insulin will improve the outcome of critically ill patients.

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