Mechanisms underlying stress-induced hyperglycemia in critically ill patients

Farshad Kajbaf¹, Mojtaba Mojtahedzadeh¹ & Mohammad Abdollahi¹†
†Author for correspondence
¹Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, PO Box 14155-6451 Iran
Tel.: +98 216 695 9104
Fax: +98 216 695 9104
E-mail: mohammad@tums.ac.ir

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Critical illnesses associate with alteration in metabolic status. Insulin resistance and enhanced blood glucose levels occur during stressful situations, such as acute illnesses. These disturbances associate with poor prognostic events. Intensive insulin therapy and maintaining normoglycemia reduce the morbidity and mortality rate in critically ill patients. We aim to give an overview of the current insights in hyperglycemia and insulin resistance in critical illnesses. A search of the literature was conducted using Pubmed articles in English. Most of the recent and relevant articles were studied, reviewed and summarized with categorization of causes, pathophysiology and adverse events. To introduce better conception regarding stress-induced hyperglycemia and its management, the most viable mechanisms and therapeutic goals are discussed. Hyperglycemia and insulin resistance are common in critically ill patients, particularly in trauma, postmyocardial infarction, following major surgery and among those with sepsis. These complications occur in patients with or without a history of diabetes. Multiple pathogenic mechanisms, such as increased release of proinflammatory cytokines and counter-regulatory hormones, have been suggested. The resulting metabolic alteration is associated with significant adverse events and poor prognostic outcomes. Strict glycemic control and intensive insulin therapy could improve the survival rate in critically ill patients. Tight glycemic control by intensive insulin therapy has a pivotal role in the treatment of such patients. Every medication or intervention that could prevent the inflammatory process and insulin resistance might be considered as therapeutic strategies for the improvement of critically ill patients with acute hyperglycemia.

Hyperglycemia in critical illnesses
The relationship between stressful situations in critically ill patients (CIPs) and acute hyperglycemia was first described in the late 19th Century [1]. Stress-induced hyperglycemia was thought of as an adaptive and even beneficial neurohormonal response to support the energy requirements of insulin-independent cell types, such as brain cells and phagocytes [1]. With high prevalence, hyperglycemia and insulin resistance are associated with poor outcome in a wide spectrum of CIPs [2-5]. Therefore, tight glycemic control could improve the prognosis of these patients and decrease adverse events.

Intensive insulin therapy & tight glycemic control in CIPs
Previously, glycemic control has not been seriously considered in the intensive care unit (ICU), except in diabetic patients or those with a persistently high glucose level above 200 mg/dl. Results from studies after 2000 demonstrated that tight glycemic control may improve the outcomes of CIPs via a reduction of systemic infection, frequency of acute renal failure requiring dialysis or hemofiltration, red blood cell (RBC) transfusion, polyneuropathy and overall hospital mortality. Currently, the use of insulin is an approved therapeutic strategy in the management of CIPs [2,3,6]. Earlier studies in diabetic patients who underwent open heart surgery or those with acute myocardial infarction (AMI) showed that hyperglycemia could be a predictor of poor prognosis [7,8]. Other clinical investigations in both medical and surgical ICUs in the diabetic and nondiabetic population have confirmed the beneficial effects of glycemic control using intensive insulin therapy [4,5,9,10].

Adverse effects of acute hyperglycemia in critical illnesses
CIPs, such as diabetic patients, are susceptible to infection due to the deleterious effects of hyperglycemia on the immune system [11]. Hyperglycemia is found to be associated with a higher risk of sepsis and septic shock among patients who need intensive care support, even for a short
period of time [12,13]. It has been demonstrated that intensive insulin therapy reduces the rate of bacteremia and wound infection in burn patients [14,15]. Control of blood glucose decreased the rate of deep sternal wound infection in diabetic patients following open heart surgery [16]. The rate of worse outcome in nondiabetic patients with acute ischemic events, such as stroke or AMI, has been reported as higher in hyperglycemic states [17–19]. In addition, hyperglycemia accompanies poor outcomes in traumatic events [20,21].

New approach to glycemic control
Several pathogenic mechanisms are thought to be involved in this metabolic phenomenon. Understanding these mechanisms would provide knowledge to better manage hyperglycemia in critical illnesses using additional therapeutic targets.

Pathophysiology of stress-induced hyperglycemia

Major causes of acute hyperglycemia
Insulin resistance and hyperglycemia are common in critical illness due to an alteration in the immunoneuroendocrine axis and subsequent alteration in lipid and carbohydrate metabolisms [1,22,23]. Disturbances in cross-taking between endocrine, immune and neural systems, which are highly interrelated with each other, and alteration in their complex interactions during critical illnesses would finally result in metabolic instabilities. Pre-existing conditions, such as diabetes mellitus (DM), pancreatitis and cirrhosis, will increase the risk of hyperglycemia in the intensive care setting [1]. Iatrogenic causes of hyperglycemia, including administration of steroids, sympathomimetics (e.g., catecholamines [ChAs]), total parenteral nutrition (TPN) and in particular, excess administration of dextrose must also be considered [1,24].

Immunoneuroendocrine alterations during acute illnesses
Indeed, stress is a response to any situation that threatens homeostasis, and usually results in the activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic autonomic nervous system [25–27].

Neuroendocrine involvements and stimulation of the HPA axis, which is characterized by hypercortisolemia during critical illnesses, play a major role in the occurrence of hyperglycemia [22,28]. Activation of the HPA axis is associated with activation of the corticotropin-releasing factor (CRF)–adrenocorticotropic hormone (ACTH) axis via cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)α, which are primed by monocytes, lymphocytes and other chief endocrine factors, and eventually results in increased secretion of glucocorticoids from the adrenal cortex, which influence the immune-accessory cells, a bidirectional interaction of immunoneuroendocrine systems [26,28,29]. Furthermore, stimulation of the sympathetic nervous system leads to release of ChAs and hormonal modulation [30,31].

Increased level of counter regulatory hormones (e.g., glucagone and growth hormone), cortisol, ChAs and proinflammatory cytokines cause insulin resistance and hyperglycemia by different mechanisms.

Counter-regulatory hormones & hyperglycemia
Blood glucose level is normally regulated by an interaction between neurohormonal and hepatic autoregulatory mechanisms. Glycogenolysis and gluconeogenesis are involved in hepatic glucose metabolisms [1,32,33]. Cortisol increases transcription of phosphoenolpyruvate carboxykinase (PEPCK) genes (the key enzyme for gluconeogenesis) and induces gluconeogenesis, in which noncarbohydrates substrates, such as lactate, alanine and glycine, are converted to glucose [34,35]. Elevated cortisol levels are observed in both acute and chronic phases of critically illneses, and occur by different neurohormonal mechanisms. It seems that there is a biphasic response to the HPA axis during the acute and protracted phases [36,37]. During the acute phase, both cortisol and corticotropin concentrations are raised due to activation of the HPA axis and steroidogenesis, which is more diverted toward glucocorticoids synthesis [25,36]. In the chronic phase (>5-day stay in ICU), corticotropine levels decrease while cortisol levels remains high [29,37].

Stimulation of the sympathetic nervous system enhances the level of counter regulatory hormones, such as epinephrine, norepinephrine, glucagon and growth hormone. ChAs increase hepatic cAMP levels, which in turn, motivate PEPCK gene transcription and increase hepatic gluconeogenesis [35]. Epinephrine promotes glycogenolysis in hepatocytes and skeletal muscle cells and, in combination with glucagon, has an additive effect on both glycogenolysis and gluconeogenesis [38]. In addition, inhibition of insulin receptor substrate (IRS)-1 activity and
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Glucose uptake can be prevented by blockade of a key role in insulin signaling [47]. Therefore, phosphatidylinositol 3 kinase (PI3K), which has aulatory hormones, which, in turn, facilitates gluconeogenesis and glycogenolysis [51].

Proinflammatory cytokines & hyperglycemia

Proinflammatory cytokines, such as TNFα, IL-1, IL-6, and IL-8, as well as counter regulatory hormones, have major roles in constitution of insulin resistance and hyperglycemia during acute illnesses.

A stress response is associated with increased secretion of proinflammatory cytokines from immune cells and other tissues, such as the gut and lung [44,45]. This immunological response activates release of counter regulatory hormones, leading to increased hepatic glucose production, decreased peripheral glucose uptake and insulin resistance in skeletal muscle and hepatocytes [2,46].

TNFα acts as an inhibitor of tyrosine kinases of insulin receptors and diminishes IRS-1 tyrosine phosphorylation in the liver and adipose tissues. In addition, TNFα impairs activation of phosphatidylinositol 3 kinase (PI3K), which has a key role in insulin signaling [47]. Therefore, translocation of GLUT4 is affected and insulin resistance occurs [48]. TNFα also activates the inhibitor κB kinase (IKK), a serine kinase that controls activation of nuclear factor (NF)-κB, which is a major proinflammatory transcription factor, and thus promotes inflammatory cascade [49,50]. TNFα also stimulates expression of hormone-sensitive lipase, resulting in increased lipolysis. Furthermore, TNFα decreases the lipo-protein lipase activity that results in mobilization of lipids from adipocytes, which appears to be another cause of insulin resistance [23]. Additionally, TNFα stimulates secretion of counter regulatory hormones, which, in turn, facilitates gluconeogenesis and glycogenolysis [51].

It has been demonstrated that IL-6 increases release of both CRH and ACTH, promoting peripheral insulin resistance and hyperglycemia [52]. Activation of IKK in hepatocytes by IL-1 results in gene expression of inflammatory cytokines via NFκB. Serine phosphorylation of IRS-1 by IKK and decreased activation of PI3K eventually suppress GLUT4 translocation. IL-1 also increases secretion of glucagon and corticostrone, which have additive effects on the production of glucose [53]. Traumatic events, such as acute brain injury, which cause hyperglycemia are associated with increased plasma levels of proinflammatory cytokines, such as IL-8 and TGF-β1 [54]. Box 1 summarizes the major causes of hyperglycemia in CIPs.

Glucose toxicity in acute illnesses

Association between hyperglycemia and poor prognostic outcome following different types of acute illnesses (e.g., AMI, stroke, trauma and complex surgery) has been well established. Hyperglycemia may be associated with hypovolemia and trace element deficiencies, leading to serious complications [1].

Hyperglycemia increases morbidity and mortality rates in CIPs through numerous different mechanisms (Box 2).

Hyperglycemia & its adverse effects

Glucose has been recognized as a proinflammatory mediator. Glycemic control exerts an anti-inflammatory effect. It has been demonstrated that glucose overfeed increases generation of reactive oxygen species (ROS) by immune cells, which results in oxidative stress [55]. ROS are involved in the pathophysiology of many complicate specialy diabetes [56,57].

In addition, glucose increases intranuclear NFκB and enhances the activator protein-1 and growth factor. These transcription factors regulate the genes that encode proinflammatory mediators [58]. Glucose also increases plasma matrix metalloproteinase (MMP)-2 and -9, which both have inflammatory properties [59].

Enhanced production of proinflammatory cytokines, such as TNFα, IL-1β and IL-6, has been observed during hyperglycemia [60-62].

Hyperglycemia, per se, promotes insulin resistance via overexpression of c-jun N-terminal kinase (JNK) and IKKβ. JNK and IKKβ, similar to mitogen-activated protein kinase and atypical protein kinase-C, are intracellular mediators of stress and inflammation and
could phosphorylate serine and threonine residues (instead of tyrosine) suppressing insulin signaling and causing insulin resistance [23,63].

Acute hyperglycemia reduces endothelial nitric oxide (NO) and promotes vascular constriction, which, in turn, causes abnormal perfusion of organs. As mentioned earlier, hyperglycemia generates ROS. However, NO that binds to superoxide radicals forms peroxynitrite and promotes platelet proaggregatory and prothrombic events [63].

An increased risk of infection is one of the consequences of hyperglycemia, possibly via disturbed immune system function [13]. Additionally, hyperglycemia weakens neutrophil function by decreasing their chemotactic and phagocytic capacity and it impairs the production of ROS and reduces the oxidative burst of leukocytes [13,64,65].

**Why is hyperglycemia profoundly fatal in critical illnesses?**

**General**

Insulin resistance is the main feature of Type 2 diabetes and an inducer of the metabolic syndrome, in which normal circulatory insulin levels are insufficient to produce an expected biological effect [66]. Insulin resistance is associated with chronic hyperglycemia, the major initiator of long-term complications and the major cause of morbidity and mortality in diabetics [67].

Why is hyperglycemia during critical illnesses more toxic acutely than in diabetic patients?

Different theories regarding acute toxicity of hyperglycemia

Some theories suggest that subtle molecular differences, patients' genetic background and differences between the acute and chronic status of hyperglycemia are interfering factors [23]. Others point out that intracellular glucose overload during critically illnesses is involved in this scenario [6].

**Glucose transporters & intracellular glucotoxicity**

It is known that glucose itself influences the regulation and expression of its cellular transporters. Downregulation of GLUTs during moderate hyperglycemia in normal cells is a protective mechanism against glucotoxicity [68]. Glucose molecules are delivered across the cell membrane by several types of transporters.

GLUT1 is needed for basal glucose uptake, even under hypoglycemic situations. GLUT2 is responsible for hepatic glucose transport and stimulates pancreas glucose-dependent insulin secretion. The GLUT4 isoform has been found in skeletal and cardiac muscles and adipose tissues, where insulin mediates glucose transport by translocation of GLUT4 to the plasma cell membrane [69,70].

Enhanced concentration of cytokines, such as TNFα, angiotensin II and endothelin-1, during the stress response stimulate the translocation and upregulation of glucose transport in different cells [71–73]. Likewise, hypoxia has the same effect on GLUTs [74]. Therefore, upregulated glucose transporters that are working without the influence of insulin cause extra influx of glucose into the cell. This leads to enhanced intracellular glucose levels in different cell types, including endothelial and epithelial cells, as well as immune cells.

**Mitochondrial disturbances & intracellular hyperglycemia**

Impaired mitochondrial function of hepatocytes has been reported during hyperglycemia [75]. This abnormality, which is not observed in skeletal muscles, reflects the direct effect of intracellular glucose toxicity, as described above. Hyperglycemia has been associated with enhanced mitochondrial superoxide production. Mitochondrial dysfunction, with a failure to produce energy for efficient metabolisms, is the major cause of cellular abnormalities and organ dysfunction leading to multiple syndromes among CIPs who die [76].

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**Box 1. Causes of hyperglycemia during critical illness.**

- Pre-existing conditions
  - Pre-existing diabetes mellitus
  - Obesity with metabolic syndrome
  - Pancreatitis
  - Cirrhosis
- Immunoneuroendocrine changes*
  - Increased level of counter regulatory hormones (e.g., epinephrine, norepinephrine, growth hormone, glucagon and cortisol)
  - Increased level of proinflammatory cytokines (e.g., TNFα, IL-1 and IL-6)
- Iatrogenic
  - Catecholamines infusion
  - TPN (particularly excess amount of dextrose infusion)
  - Drugs (e.g., corticosteroids, thiazide diuretics and phenytoin)
- Hypokalemia (impairs insulin secretion)

*These metabolic alterations increase the rate of glycogenolysis and gluconeogenesis and induce insulin resistance in skeletal muscles, adipose tissues and liver. IL: Interleukin; TNF: Tumor necrosis factor; TPN: Total parental nutrition.
Mitochondrial dysfunction is also attributed to insulin resistance. As a result of decreased oxidation of mitochondrial fatty acids, intracellular fatty acyl coenzyme A and diacyl glycerol levels are enhanced. Thus, atypical protein kinase C, JNK and IKKβ are activated to block IRS-1 tyrosine phosphorylation causing insulin resistance [77].

Benefit of glycemic & nonglycemic effects of intensive insulin therapy

Generally, intensive glycemic control improves the survival of CIPs and decreases morbidity and mortality rates. Insulin has a multitude of favorable metabolic and nonmetabolic effects that could reverse almost all undesirable adverse effects of stress response and prevent glucotoxicity (Box 3).

Insulin & its anti-inflammatory properties

Insulin has a potent anti inflammatory effect [63]. It has been demonstrated that insulin decreases intranuclear NFκB and enhance IkB levels in mononuclear cells [78]. Additionally, insulin suppress the actions of pro-inflammatory transcription factors early growth response-1 and activator protein-1. It also reduces MMP-2 and -9, which are important components of inflammation [79]. Insulin could reduce mannose-binding lectin and C-reactive protein, which would result in anti-inflammatory effects [80].

Insulin & the cardiovascular system

Hyperglycemia promotes thrombosis by activation of tissue factors, while insulin reverses that by suppressing tissue factor, plasminogen activator inhibitor-1 and pro-MMP-1. MMP-1 motivates prothrombic process by activation of protease-activated receptor-1, which mediates the action of thrombin [81,82].

Insulin also increases the release of NO from the endothelium and increases the synthesis and expression of NO in endothelial cells and platelets. Vasodilatation and inhibition of platelet aggregation are other non-metabolic benefits of insulin [23,83]. In oxidative stress, ROS increases and peroxynitrate is formed, which depresses mitochondrial function. Since insulin reduces the NO level and decreases inducible nitric oxide synthase (iNOS) expression, it would protect mitochondrial function and prevent systemic inflammation [83]. It has been demonstrated that insulin has antiapoptotic and cardioprotective effects that are mediated by activation of the Akt–PI3K pathway and suppression of proinflammatory cytokines. In addition, insulin promotes the synthesis of endothelial NOS (eNOS) and enhances anti-inflammatory process that eventually lead to preservation of myocardial integrities and protect on of infracted areas from ischemic reperfusion injuries [84,85].

Insulin & lipid profile

Lipotoxicity in hepatocytes and skeletal muscles is also involved in insulin resistance [66]. Insulin therapy in CIPs decreases serum triglyceride and FFA levels, while it increases high-density lipoprotein level. Therefore, insulin therapy improves the lipid profile [6,86,87].
Stress precipitates release of counter regulatory hormones by activation of the HPA axis and enhances the release of proinflammatory cytokines from immune cells. These proinflammatory cytokines activate the CRF–adrenocorticotropic hormone axis. In addition, stress increases extraction of alanine and lactate (two major gluconeogenesis substrates) from skeletal muscle. Conversely, counter regulatory hormones stimulate PEPCK (the key enzyme for gluconeogenesis) activity and expression, thus hepatic glucose output increases. Likewise, FFA and triglyceride levels increase by stimulation of counter regulatory hormones and the effect of glucose on adipose tissue. Glucose has deleterious effects on the immune system and skeletal muscle (e.g., hyperglycemia exacerbates muscle protein catabolism). Mitochondrial dysfunction and increased generation of ROS, which lead to oxidative stress, occur during hyperglycemia. Glucose promotes insulin resistance and has inflammatory properties and enhances proinflammatory cytokines secretion by promotion of transcriptional cofactors, such as NFκB, which regulate the proinflammatory mediators’ genes. FFA, triglyceride, counter regulatory hormones and proinflammatory cytokines induce insulin resistance by different mechanisms and prevent glucose uptake, which results in acute hyperglycemia.

ACTH: Adrenocorticotropic hormone; CRF: Corticotropin-releasing factor; FFA: Free fatty acid; HPA: Hypothalamic–pituitary–adrenal axis; NF: Nuclear factor; PEPCK: Phosphoenolpyruvate carboxykinase; ROS: Reactive oxygen species.
Discussion

Insulin or glycemic control?

Among all the clinical investigations, it is yet questionable whether it is insulin itself or glycemic control, or perhaps both, that influence the positive fate of CIPs and their outcomes. Although insulin has its unique therapeutic effects in CIPs, the mortality rate appears to be higher among patients who receive higher doses of insulin in order to reach euglycemia [88].

As described previously, cytokine storms and over-release of ChAs during the disturbed stressful condition in critical illnesses results in insulin resistance. This occurs through destruction of subcellular insulin signaling components or by affecting insulin receptor sites [1,2,22,23].

Probable therapeutic targets & new therapeutic strategies

TNFα, among cytokines, and NFκB, among proinflammatory transcription factors, can be considered as therapeutic targets. The role of insulin-sensitizing agents, such as metformin and thiazolidinediones, in the management of Type 2 diabetes is obviously clear. These drugs, besides their effects on the reduction of insulin resistance, have the potential for anti-inflammatory properties. For example, troglitazone decreases the cellular level of NFκB and stimulates IkB with a beneficial effect on the suppression of inflammatory process [89]. Likewise, metformin can exert a direct vascular anti-inflammatory effect by inhibiting NFκB through blockade of the PI3K–Akt pathway [90].

The safety and efficacy of metformin or thiazolidinediones have not been proven among CIPs. Although it has been demonstrated that metformin has a beneficial effect on the survival of burn patients by increasing the glucose clearance either due to enhanced insulin sensitivity or increasing insulin availability, more clinical trials must be designed [91]. An other valuable action of metformin is the improvement of muscle protein kinetics that occurs in combination with insulin in burn patients [92].

In addition, metformin activates AMP-activated protein kinase [93,94], the major cellular regulatory factor in lipid and glucose metabolism and even has an indirect effect on insulin sensitivity in adipose and skeletal muscles [95,96].

Lactic acidosis is a matter of concern during metformin therapy in diabetic patients and it is controversial as to whether metformin causes lactic acidosis [97,98].

Outlook

Generally, the stress response is recognized as a programed and adaptive process for survival advantages in drastically disturbed physiological situations, such as acute illness. Stress triggers systemic inflammatory processes that accompany secondary complications, such as acute hyperglycemia and insulin resistance. Stress-induced hyperglycemia has a direct proportion to the morbidity and mortality rates in critical illnesses.

Intensive insulin therapy and glycemic control have remarkable positive effects on the outcome of CIPs. Downregulation of insulin receptor and

Highlights

- Insulin resistance and hyperglycemia occur in critical illnesses due to an alteration in the immunoneuroendocrine axis and subsequent alteration in the metabolism of lipid and carbohydrate.
- Increased levels of counter regulatory hormone and proinflammatory cytokines cause insulin resistance and hyperglycemia. This happens by increasing the rate of glycogenolysis and gluconeogenesis, interrupting the components of the insulin-signaling pathway and impairing insulin-mediated glucose uptake.
- Glucose has proinflammatory properties and glucose overfeed increases the generation of reactive oxygen species by immune cells, resulting in oxidative stress and promoting proinflammatory cytokine cascade. Likewise, hyperglycemia per se promotes insulin resistance.
- During critical illnesses, extra influx of glucose into endothelial, epithelial, hepatocytes and immune cells leads to enhanced intercellular glucose levels, which intensify cellular inflammation and impair mitochondrial function.
- Intensive glycemic control reduces morbidity and mortality rates. Insulin has a multitude of favorable metabolic and nonmetabolic effects that could reverse almost all undesirable events of stress response and prevent glucotoxicity.
- Almost all components of the systemic inflammatory response could be considered as therapeutic targets since they are directly and indirectly involved in this event.
- Every medication or intervention, such as insulin-sensitizing agents, which could prevent inflammatory process and insulin resistance might be considered as therapeutic strategies in improving critically ill patients.
impaired insulin function deteriorate insulin resistance via proinflammatory cytokines and ChAs. Therefore, clinicians have to use increasingly more insulin to overcome the hyperglycemia. Cautious measurement of blood glucose is necessary when insulin is used continuously. Finally, the need for the development of new curative protocols to alleviate hyperglycemia and to control systemic inflammatory response is obviously required.

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