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SYMPOSIUM

Hyperglycemia in Critical Illness: A Review

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Abstract

Hyperglycemia is commonplace in the critically ill patient and is associated with worse outcomes. It occurs after severe stress (e.g., infection or injury) and results from a combination of increased secretion of catabolic hormones, increased hepatic gluconeogenesis, and resistance to the peripheral and hepatic actions of insulin. The use of carbohydrate-based feeds, glucose containing solutions, and drugs such as epinephrine may exacerbate the hyperglycemia. Mechanisms by which hyperglycemia cause harm are uncertain. Deranged osmolality and blood flow, intracellular acidosis, and enhanced superoxide production have all been implicated. The net result is derangement of endothelial, immune and coagulation function and an association with neuropathy and myopathy. These changes can be prevented, at least in part, by the use of insulin to maintain normoglycemia.

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Introduction

Hyperglycemia is a common occurrence in the intensive care unit (ICU) and is associated with worse outcomes in both adults and children.[1,2] Aggressive correction of hyperglycemia using insulin reduces morbidity and mortality in multiple acute stressful situations. This has been demonstrated in prospective randomized trials in intensive care,[3,4] coronary care,[5] and perioperatively.[6–8] As a result, glycemic control has been widely accepted into clinical practice[9] and is routinely included in international treatment guidelines.[10] However, the consequent risk of an increase in detrimental hypoglycemic episodes[11] may be responsible for the lack of benefit, or even harm, shown in some recent studies.[12,13] While some have questioned the efficacy of "tight" glycemic control, nonetheless all remain in agreement that hyperglycemia should be avoided. This review examines the mechanisms underlying hyperglycemia, putative mechanisms by which it causes harm, and, briefly, the effects of insulin therapy with particular relation to hypoglycemia.

Cellular Glucose Uptake

In health, cellular glucose uptake is via either insulin- or noninsulin-dependent mechanisms. The latter account for up to 80% of total glucose uptake[14] and are directed largely at the central nervous system. The remaining

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Abbreviations: (ADMA) asymmetric dimethylarginine, (eNOS) endothelial-derived nitric oxide synthase, (GAPDH) glyceraldehyde-3-phosphate dehydrogenase, (GH) growth hormone, (GLUT) glucose transporter, (ICAM-1) intercellular adhesion molecule-1, (ICU) intensive care unit, (IGF) insulin growth factor, (IGFBP) insulin-like growth factor-binding protein, (IL) interleukin, (iNOS) inducible nitric oxide synthase, (IRS) insulin receptor substrate, (JNK) c-jun N-terminal kinase, (MAPK) mitogen-activated protein kinase, (NADH) nicotinamide adenine dinucleotide, (NF) nuclear factor, (NO) nitric oxide, (NOS) nitric oxide synthase, (PARP) poly-ADP ribose polymerase, (PEPCK) phosphoenolpyruvate carboxylase, (PI-3-kinase) phosphoinositide-3-kinase, (PKC) protein kinase C, (PPAR) peroxisome proliferator-activator receptor, (TNF) tumor necrosis factor

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20% is mediated by insulin, 50% of which is accounted for by muscle cells. As glucose is a polar molecule, its transport into cells is mainly by active (gut and kidney) or facilitated diffusion. Most glucose uptake by cells is facilitated by glucose transporters (GLUT), a family of specialized transmembrane proteins. At least 13 isoforms have been identified so far, although GLUT 1–4 are the most important clinically.

	Location	Notes
GLUT-1	Widespread	Responsible for basal glucose uptake. Insulin independent
GLUT-2	Renal tubules, small intestine, liver, and pancreatic β cells	Ensures rapid glucose uptake by liver. Insulin independent
GLUT-3	Neurons and placenta	Possibly most important isoform in the central nervous system. Insulin independent
GLUT-4	Adipose, skeletal, and cardiac muscle	Located intracellularly, moving to plasma membrane promoted by insulin

Under normal conditions, blood glucose levels are heavily regulated by the neuroendocrine system. Most glucose production occurs within the liver, either through glycogenolysis or through gluconeogenesis, although the kidney can also make significant contributions. In the post-absorptive state, between 20 and 42% of glucose release is through gluconeogenesis and 20% of removal is renal derived.[15]

Control of Blood Glucose Levels

The control of blood glucose is complex, involving interactions among the pituitary, liver, pancreas, and adrenals. Insulin acts to lower blood glucose, enhancing glucose uptake and glycogen synthesis and suppressing gluconeogenesis. However, hormones such as glucagon, catecholamines, growth hormone (GH), and cortisol raise blood glucose concentrations through upregulation of glycogenolysis and gluconeogenesis. This is a necessary endogenous response to a stressful situation such as injury or infection, mobilizing glucose to enable increased cellular metabolic requirements. Secretion of these hormones results from activation of the sympathetic nervous system or direct stimulation by proinflammatory mediators. Cytokines such as tumor necrosis factor (TNF)α and interleukin (IL)-1 can stimulate the hypothalamic–pituitary axis directly, releasing the adrenocorticotrophic hormone, whereas IL-1 and IL-2 can stimulate the adrenal cortex to enhance glucocorticoid synthesis.

Both the liver and islet cells of the pancreas can respond directly to the blood glucose concentration, allowing a degree of autoregulation (reviewed elsewhere[16]). An intricate neural network also exists to maintain control over the different organs involved.[17] Glucose-sensitive neurons within the ventromedial hypothalamus (satiety center) increase their firing rates when glucose is applied directly, whereas those within the lateral hypothalamus (feeding center) depress their activity. This results in activation of the pancreatic branch of the vagus nerve, leading to subsequent insulin release and a reduction in activity of the sympathoadrenal system. A strain of rat genetically determined to become obese and diabetic has an impairment within the vagal pancreatic efferent, resulting in an impaired insulin response to a glucose load.[18] These pancreatic efferents, as well as intestinal efferents, may also be stimulated rapidly by sweet gustatory afferents from the tongue. Hepatic denervation also results in hyperglycemia,[19] which can be restored in animal models by intraportal, but not peripheral, acetylcholine. In insulin-deficient mice, neural networks may be responsible for cross-talk between the liver and pancreas, with liver-derived extracellular regulated kinase resulting in an increased β-cell mass.[20]

Hyperglycemia in Critical Illness

Hyperglycemia was first recognized during episodes of stress by Thomas Willis in the 17th century. Although identified as an appropriate short-term physiological response to injury, the goalposts have been shifted in recent decades by the advent of critical care. This has enabled prolonged survival of patients in a critically ill state, and thus an extended period of stress to which the human body maladapts. This is compounded by the use of feeds, fluids, and drugs that raise sugar levels directly or are counterregulatory to insulin. Mechanisms underlying hyperglycemia are complex but include the following.

1. Peripheral and hepatic insulin resistance.
2. Enhanced hepatic and renal glucose production.
3. High glucose loads from feeds and intravenous infusions.

Insulin Resistance

Insulin resistance is a well-recognized phenomenon in critically ill patients.[21–23] It is characterized by raised plasma levels of insulin,[22,24] organ-specific alterations in glucose utilization, and impaired insulin-mediated uptake. The degree of insulin resistance correlates with both illness severity and mortality.[25]

The inflammatory cascade is clearly implicated in the pathogenesis of insulin resistance. Infusion of TNFα into rats resulted in an inability of insulin to suppress hepatic glucose production and enhance peripheral uptake.[26] Rats treated with the proinflammatory agent zymosan demonstrated both hepatic and muscle (skeletal, heart, and diaphragm) insulin resistance that could be prevented by pretreatment with anti-TNF antibodies.[27] TNFα, applied to a cell culture, decreased insulin-mediated 2-deoxyglucose uptake and impaired insulin-signaling mechanisms.[28] This impairment resulted from a decrease in the ability of insulin receptor substrates (IRS)-1 and -2 to stimulate protein kinases, plus an inhibition of mitogen-activated protein kinases (MAPK) p42 and p44.

When exposed to endotoxin, knockout mice deficient in the proinflammatory cytokine macrophage migration inhibitory factor demonstrated significantly less perturbation in blood glucose levels and increased adipocyte glucose uptake compared to wild-type animals.[29] Myocytes exposed to TNFα, interferon-γ, and lipopolysaccharide demonstrated an increased turnover of glucose mediated by increased expression of the GLUT-1 transporter.[24] However, these cells were "resistant" to the effects of insulin, which was associated with a loss of GLUT-4 transporters. Inhibition of nitric oxide (NO) synthesis reversed the sensitivity to insulin, suggesting that additional mechanisms are involved. An increase in glucose uptake was also noted in healthy volunteers 5 hours after administration of lipopolysaccharide[30] and in rats infused with TNFα.[26]

The insulin resistance witnessed in critical illness generally persists well beyond the time course of most pro-inflammatory mediators, suggesting that their role is indirect. However, resistin, a proinflammatory cytokine derived in part from monocytes,[31] tends to remain elevated in patients with severe sepsis over the course of their illness. Higher levels of resistin have been associated with raised blood glucose in both septic patients and mice.[32]

Due to its mass, skeletal muscle is considered the probable site of peripheral insulin resistance; however, resistance is not uniform across insulin-sensitive cells. In a rat study, sepsis impaired insulin-mediated glucose uptake in gastrocnemius and quadriceps muscles but with relative sparing of abdominal muscles and diaphragm.[33] Because the insulin sensitivity of skeletal muscle increases with improved tissue perfusion in normal subjects,[34] it could be argued that the insulin resistance witnessed during times of shock may be a reflection of poor perfusion. Nevertheless, several papers report insulin resistance that is independent of blood flow.[33,35]

Mechanisms underlying insulin resistance occur at several levels:

1. *The insulin receptor*. Data on insulin receptor levels are contradictory. Hepatic and skeletal muscle insulin receptor levels were unchanged in a septic rat model.[36] Fan and colleagues[37] also demonstrated that neither the number nor the affinity of insulin-binding sites was altered in the muscle of lipopolysaccharide-treated rats. Likewise, a rat hemorrhage model used to investigate insulin resistance demonstrated no change in insulin receptor (or IRS-1) protein levels or function.[38] However, a longer term endotoxic rat model (over 3 days) did demonstrate 37% less insulin receptors than controls.[39]

2. *Insulin receptor substrate and phosphoinositide-3-kinase (PI-3-kinase)*. TNFα activates protein kinase B, inducing serine phosphorylation of IRS-1. This, in turn, inhibits insulin receptor tyrosine kinase, thereby reducing glucose uptake by the cell. In animals given lipopolysaccharide, there was a marked reduction in tyrosine phosphorylation of the insulin receptor IRS-1 and MAPK[37,40] compared to controls. McCowen *et al.*[39] also demonstrated impaired tyrosine phosphorylation and reduced levels of the insulin receptor in a long-term lipopolysaccharide rat model. IRS-1 and -2 levels were lower, and there was a reduced interaction between IRS-1 and PI-3-kinase. These findings were present at 3 days (but not at 4 hours) in both liver and skeletal muscle. Others have demonstrated tissue-specific changes,[36] with lower IRS-1 levels and a reduced IRS-1/PI-3-kinase interaction in skeletal muscle (but not in the liver) of septic rats. Serine phosphorylation of IRS-1 may be partly prevented by the use of aspirin, possibly through its inhibition of c-jun N-terminal kinase (JNK).[41]

3. *c-jun N-terminal kinase*. JNK is a serine kinase and a member of the MAPK family. JNK acts by phosphorylating the proteins c-Jun and JunB that are involved in cell development. JNK1 has three isoforms and is thought to play a role in insulin resistance by promoting the

serine phosphorylation of IRS-1, thereby reducing its action on PI-3-kinase. In healthy volunteers, adipocyte JNK1/2 activity demonstrated a direct correlation with insulin resistance.[42] Mitochondrial dysfunction, which occurs in both septic animals and patients,[43,44] is associated with increased levels of JNK activity, IRS-1 serine phosphorylation, and impaired glucose uptake in adipocytes.[45] Inhibiting JNK expression reversed these changes and restored glucose uptake. Lim and associates[46] also found that mitochondrial dysfunction in hepatocytes was associated with an increase in cytosolic calcium, activation of JNK, and upregulation of the gluconeogenic enzyme phosphoenolpyruvate carboxylase (PEPCK). JNK-knockout mice and diabetic mice given a JNK inhibitor both showed decreased insulin resistance.[47]

4. *Peroxisome proliferator-activator receptor (PPAR) γ.* PPARs are a group of nuclear receptor proteins that regulate gene expression and are important in regulating metabolism and cell differentiation. Activated PPARs create heterodimers with the retinoid-X-receptor. These are bound to response elements within the promoter regions of certain genes, including those encoding for adiponectin, a hormone capable of sensitizing cells to the action of insulin. The thiazolidinedione class of drugs acts as PPAR agonists, whereas TNFα, hypoxia, and insulin-like growth factor-binding protein (IGFBP)-3[48] have the ability to inhibit PPAR activation, although by mechanisms that remain uncertain (reviewed elsewhere[49,50]).

Hepatic insulin resistance is associated with a fall in insulin growth factor (IGF)-1 levels in both critically ill children and adults, with nonsurvivors having particularly low levels.[51] IGF-1 (known previously as somatomedin C) is a polypeptide hormone similar in structure to insulin that binds to the widespread IGF and insulin receptors. IGF-1 is created mainly in the liver; its production is stimulated by GH and inhibited by malnutrition. The circulating form is bound mainly to one of the six insulin-like growth factor-binding proteins. The effects of IGF-1 are similar to insulin and it acts as a promoter of cell growth.

During critical illness, GH levels rise significantly,[51,52] particularly in nonsurvivors. This is due, at least in part, to direct stimulation of the pituitary gland by pro-inflammatory cytokines.[53] Binding of the GH to its transmembrane receptor results in formation of a complex with a tyrosine kinase, janus kinase 2. This causes phosphorylation of the signal transducer and activator of transcription 5, which, in turn, results in the transcription of GH-inducible genes, including IGF-1. The liver does, however, appear to be resistant to the effects of GH while IGF levels remain low. This disturbance in the GH/IGF-1 response may possibly mediate the marked muscle wasting witnessed during critical illness. The reason for this disturbance is unclear. Investigators have shown, albeit not consistently,[54] a fall in hepatic GH receptors[55] and a disruption of downstream signaling. This disruption may be secondary to an upregulation of inhibitory proteins by proinflammatory cytokines.[54,56] To circumvent this resistance, GH was administered to critically ill patients, but this strategy was unfortunately associated with excess mortality.[57] Of note, IGF-1 administration improved splenocyte function[58] and survival[59] in septic mice and increased skeletal muscle protein synthesis in septic rats.[60]

The depletion of IGF-1 witnessed in critical illness may be partly mediated by decreased IGF-1 synthesis; TNFα suppresses IGF-1 mRNA and impairs the response to GH.[61] This effect was unresponsive to the inhibition of either nitric oxide synthase (NOS) or nuclear factor (NF)-κB. Further work suggests that the effects of TNFα are mediated via phosphorylation of c-jun, inhibition of which could negate the effects of TNFα on IGF-1 mRNA. The use of anti-TNFα antibodies attenuated the fall in plasma and liver IGF-1 in a rat endotoxin model.[62]

Low IGF-1 levels may also result from upregulation and increased affinity of its binding protein, IGFBP-1, thereby reducing the free active portion. Derived mainly from hepatocytes, IGFBP-1 is up- and downregulated rapidly by the cellular metabolic status. Transcription is repressed rapidly by insulin and stimulated by hepatic substrate deprivation. However, this regulation is disrupted during critical illness, particularly in nonsurvivors.[51,63] Patients treated with insulin to maintain strict glycemic control showed no repression of IGFBP-1 compared to those treated with a more liberal regimen. IGFBP-1 remained elevated in long-stay ICU patients despite adequate feeding, although levels did fall in those who survived.[63] Similar findings of low IGF-1 and high IGFBP with decreased sensitivity to insulin are found in patients with cirrhotic liver disease.[64] Here, Mesotten and colleagues[63] described an inability of insulin to suppress the transcription of hepatic PEPCK, the rate-limiting step in gluconeogenesis normally suppressed by insulin. Although a rise in IGFBP-1 is well recognized in critical illness, other IGFBPs may be affected differently. In a mouse sepsis model, IGFBP-5 was decreased in skeletal muscle[65] in response to TNFα whereas IGFBP-4 was unchanged. The mechanism(s)

resulting in raised levels of IGFBP-1 also remains unclear. High levels of glucagon or cortisol elevate IGFBP-1 levels, although plasma cortisol levels tended to normalize in those undergoing prolonged stays in intensive care. IL-1 and TNFα increase IGFBP-1 protein and hepatic mRNA levels in mice,[66] even in those that have undergone prior adrenalectomy.

Glucose Production and Utilization

Critical illness is associated with both enhanced glucose production and utilization. Production is mainly the result of augmented hepatic gluconeogenesis but also occurs via glycogenolysis and reduced glycogen synthesis. Although often overlooked, renal-derived glucose (gluconeogenesis) may also be important; it accounts for 27% of glucose appearance in health but 40% in response to epinephrine.[15] The main precursors for renal gluconeogenesis are lactate and glycerol.[67] Increased glucose turnover is evident in patients with septic or cardiogenic shock.[68] In burn patients,[69] glucose production was increased by 160%. This was thought to be due to enhanced hepatic gluconeogenesis associated with increased hepatic lactate, pyruvate, and alanine uptake. Glugoneogenesis was further enhanced by bacteremia. However, in bacteremic burn patients complicated by multiorgan dysfunction, hepatic amino acid uptake and glucose production began to fall. This may explain the hypoglycemia that occasionally complicates the course of sicker patients. In a septic rat model, Lang and colleagues[70] showed a 42% increase in glucose turnover. The majority of glucose was recycled from gluconeogenic precursors, particularly lactate.

Despite the insulin resistance discussed earlier, critical illness is associated with enhanced glucose utilization (noninsulin mediated), possibly as a result of increased quantity and activity of the GLUT-1 transporter. Fibroblasts exposed to IL-1 increased glucose uptake to a degree that correlated with an increasing quantity of the glucose transporter.[71] TNFα infusions in rats raised whole body glucose production and utilization by 133%.[26] Liver, spleen, gut, skin, lung, and muscle all showed marked increases in glucose uptake, with brain being the only organ unaffected. Similar findings were demonstrated in a septic rat model in which the authors postulated the majority of the increased uptake was by mononuclear phagocytes.[72] A short-term lipopolysaccharide rat model demonstrated raised glucose utilization throughout the entire gastrointestinal tract that was independent of insulin, plasma glucose, or TNFα levels.[35]

Finally, the hyperglycemia witnessed in critical illness may be compounded further by excessive calorie intake administered by the physician, a significant portion of which may be carbohydrate based.[73] This could be partly alleviated by the choice of low carbohydrate feeds.[74] In addition, the use of drugs such as catecholamines and corticosteroids will also produce hyperglycemia.

Effects of Hyperglycemia

Hyperglycemia was reported as being present in up to 68% of patients admitted to a medical ICU.[75] It is an independent predictor of death in many acute settings, including acute myocardial infarction,[76] trauma, head injury,[77,78] and stroke. Postulated mechanisms by which hyperglycemia causes harm include decreased cerebral blood flow, intracellular acidosis, and low ATP levels; these may be similar to the actions of hyperglycemia witnessed in diabetes mellitus.[79] Cells damaged by hyperglycemia are primarily those unable to effectively control their intracellular glucose concentration. These include neuronal, capillary endothelium, and renal mesangial cells. Raised intracellular glucose levels result in an increased flux through the glycolytic pathway and the Krebs cycle, resulting in an increased production of the reducing equivalents, nicotinamide adenine dinucleotide (NADH) and succinate. These, in turn, "donate" electrons to the mitochondrial respiratory chain that contains four enzyme complexes. Electrons pass down the chain, finally reducing oxygen to water at complex IV. The passage of electrons enables the pumping of hydrogen ions across the inner mitochondrial membrane, generating a pH/proton gradient. This gradient is then used by the transmembrane enzyme ATP synthase to produce ATP. The magnitude of this gradient is related to superoxide production[80] and is normally tightly controlled. In hyperglycemic states, the increased production of NADH and succinate results in increased superoxide production. This may be enhanced yet further by direct damage to mitochondrial complexes by either hyperglycemia[81] or sepsis.[43] Superoxide has the ability to damage DNA with the resultant activation of poly-ADP ribose polymerase (PARP). This, in turn, inhibits glyceraldehyde-3 phosphate dehydrogenase (GAPDH), an enzyme involved in a diverse array of functions, including glycolysis.[82] Maintaining normoglycemia with insulin in an endotoxic rat model reduced the activation of PARP.[83] Inhibition of GAPDH enables an accumulation of upstream metabolites and the activation of four damaging pathways (reviewed elsewhere[79]).

1. *Increased protein kinase C (PKC) activity*. PKC can upregulate NF-κB, a transcription factor that controls many proinflammatory genes. NF-κB is upregulated even after short episodes of hyperglycemia.[84] The resulting expression of proinflammatory genes may persist for many days after the resolution of hyperglycemia. PKC also results in downregulation of endothelial-derived nitric oxide synthase (eNOS) and upregulation of endothelin-1 with a consequent disruption of microvascular control.

2. *Increased hexosamine pathway flux*. Raised intracellular glucose results in an increased glycolytic flux, which increases amounts of *N*-acetyl glucosamine. This compound alters transcription factors and hence gene expression, for example, upregulating plasminogen activator inhibitor-1.

3. *Increased advanced glycation end product formation*. These molecules can alter proteins involved in gene transcription and the extracellular matrix.

4. *Increased polyol flux*. When intracellular glucose levels are high, a proportion is reduced to sorbitol by the action of aldose reductase, an enzyme not normally involved in glucose metabolism. Aldose reductase competes for the cofactor NADPH with glutathione reductase, thereby depriving the cell of reduced glutathione, an important antioxidant.

Hyperglycemia is a risk factor for infection and is associated with increased mortality in acute illness.[85–87] It is associated with an increased risk of acquiring pathogenic bacteria within the bronchial tree of intubated patients,[88] whereas patients with diabetes are more prone to infected surgical wounds, foot ulcers, and infective diarrhea. The relative bacterial overgrowth witnessed in hyperglycemia may be partly due to altered host defenses. Hyperglycemia reduces polymorphonuclear leukocyte chemotaxis and bactericidal ability in diabetes patients.[89] Impaired leukocyte phagocytosis in patients with diabetes has also been reported.[90,91] Diabetic rat studies have demonstrated an impairment in T-cell-mediated responses.[92] Blood taken from hyperglycemic healthy volunteers exposed to endotoxin showed reduced IL-1 and NF-κB expression[93] and impaired neutrophil activity.[94]

A raised blood glucose level is also recognized as being proinflammatory and pro-oxidant. Mononuclear cells isolated from healthy volunteers revealed higher levels of NF-κB binding activity, raised reactive oxygen species,[95] and increased levels of TNFα mRNA[96] following exposure to a raised blood glucose level. Glucose fluctuations in patients with type 2 diabetes mellitus were associated with increased urinary 8-iso prostaglandin $F_{2\alpha}$, a marker of oxidative stress.[97] Plasma IL-6 and IL-10 levels and lactate were also significantly higher in septic diabetic rats compared to nondiabetic animals.[98]

In a rabbit burn model,[99] hyperglycemia was associated with a rise in NO levels, enhanced aortic eNOS, and muscle inducible nitric oxide synthase (iNOS) expression (but lower NOS activity) and impaired endothelial function. The use of insulin to decrease blood sugar prevented these changes, an effect thought to be due to maintaining normoglycemia rather than a further action of insulin. The authors also demonstrated that hyperglycemia raised levels of the natural NOS inhibitor asymmetric dimethylarginine (ADMA),[100] a finding associated with increased mortality. In similar models, the hyperglycemia associated with burns was associated with weight loss, lactic acidosis, impaired monocyte phagocytosis, and impaired renal and liver function; this could be ameliorated by controlling glucose levels with insulin.[101,102] The rise in ADMA in critically ill patients could be partly ameliorated by the use of insulin.[103] Markers of endothelial activation [intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, and von Willebrand factor] were raised in healthy volunteers exposed to endotoxin but were similar in those rendered hyperglycemic compared to normoglycemic controls.[94] However, others have demonstrated that tight glycemic control does reduce endothelial activation in critically ill patients,[104] with lowered levels of circulating ICAM-1 and E-selectin, possibly occurring through a reduction in iNOS expression.

Hyperglycemia also produces a hypercoaguable state partly through the increased expression of tissue factor, which is both procoagulant and proinflammatory. It activates factor VII of the coagulation cascade, ultimately resulting in the generation of thrombin, a protease capable of converting fibrinogen to fibrin and activating platelets. Activation of human mononuclear cells by hyperglycemia was associated with an increased expression of tissue factor.[105] Mononuclear tissue factor is also upregulated on exposure to endotoxin.[106] Healthy volunteers rendered hyperglycemic and exposed to endotoxin demonstrated evidence of a procoaguable state with raised plasma levels of soluble tissue factor and thrombin–antithrombin complexes when compared to normoglycemic controls.[94]

Furthermore, hyperglycemia is associated with poor gut motility, a factor that may be important in bacterial overgrowth and translocation. A rat model of endotoxemia

demonstrated that hyperglycemia was associated with a deterioration in gut barrier function and increased bacterial translocation.[107] This dysmotility may be in part due to the inhibitory effects of hyperglycemia on vagal nerve activity.[108] The aggressive management of hyperglycemia in patients reduced the incidence of critical illness polyneuropathy and myopathy.[109] Liver samples taken at autopsy from patients dying from multiorgan failure demonstrated that those patients treated with insulin to meet strict glycemic targets had less mitochondrial ultrastructural damage and greater respiratory chain complex activity compared to those with more liberal targets.[110]

Hypoglycemia

The usual clinical manifestations of hypoglycemia—hunger, fear, sweating, tachycardia, personality change, or seizures—are often difficult to interpret in the critically ill patient, especially if sedated and ventilated. Although well recognized that prolonged or severe hypoglycemia is associated with permanent neurologic damage, there are little data to indicate how critically ill patients respond to such an insult.

A major problem in achieving tight glycemic control with insulin is hypoglycemia, which, in itself, carries a risk of complications.[11] In a meta-analysis of 8432 critically ill adults, the risk of hypoglycemia with tight glycemic control was 13.7% vs 2.5% in the control group.[111] In a recent, large randomized control trial investigating the efficacy of tight glycemic control in the critically ill, severe hypoglycemia was reported in 6.8% in the protocol arm vs 0.5% in the control arm.[13] Although less frequent than hyperglycemia, hypoglycemia may also be part of the disease process.[112,113] It is more common in those with sepsis, renal failure, or malignancy[113] and is associated with worse outcomes. Tight glycemic control in traumatic brain injury is associated with lower cerebral glucose levels and raised glutamate and lactate:pyruvate ratios.[114] Persistently low extracellular glucose levels were associated with a worse clinical outcome.[115]

Summary

In conclusion, hyperglycemia causes harm through a variety of mechanisms, and this damage is accentuated in the critically ill where there is concurrent activation of multiple inflammatory processes. There is broad consensus that hyperglycemia should be avoided, although optimal treatment end points remain to be clarified. Certainly, hypoglycemia should be avoided.

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