# Hyperglycemia in Critically Ill Patients

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**ABSTRACT:** Hyperglycemia is common in critically ill humans. Recent clinical trials have shown a significant reduction in morbidity and mortality rates with the use of intensive insulin therapy to maintain strict normoglycemia in critically ill patients. Hyperglycemia is associated with many detrimental effects, including reduced immune function, increased inflammation and coagulation, and modulation of the endothelium. Most of the evidence regarding the adverse effects of hyperglycemia is derived from humans with diabetes, cardiac failure, or traumatic brain injury. In addition to its anabolic effects on metabolism, insulin has antiinflammatory properties. To define the potential risks and benefits of intensive insulin therapy in critically ill animals, prospective, randomized clinical trials are necessary.

Recent human clinical trials[1–4] have shown a significant reduction in morbidity and mortality rates in a wide range of critically ill patients when insulin therapy is used to maintain normoglycemia within a narrow range (80 to 110 mg/dl). Specific subpopulations in which glycemic control appears to be of particular importance include patients with cardiac disease, neurotrauma, or sepsis. The mechanism(s) associated with the detrimental effects of hyperglycemia and the improvement associated with strict glycemic control are currently under investigation. This article reviews the normal mechanisms of glucose control, causes of hyperglycemia in critically ill patients, potential detrimental effects of hyperglycemia, and implications for clinical veterinary practice.

## NORMAL GLUCOSE METABOLISM

Glucose is produced from carbohydrate digestion in the small intestine, glycogenolysis in muscle and the liver, gluconeogenesis in the liver resulting from glycerol fat mobilization, amino acid breakdown, and lactate metabolism through the Cori cycle[5] (Figure 1).

Normoglycemia is important for cellular function. For glucose to be transported into a cell, it must bind to one of several available carrier proteins, which then work through an active or a passive transport mechanism. One active carrier is the sodium–glucose cotrans-

porter, which is used for glucose uptake in the proximal tubule of the kidneys and in the small intestine.[6] Several glucose transport proteins (GLUTs) use facilitated diffusion.[7] GLUT 1 is responsible for basal glucose uptake and is especially important in the brain and placenta.[8] The high glucose affinity of GLUT 1 ensures transport during hypoglycemia.[7] GLUT 2, which is found in the liver, kidneys, small intestine, and pancreatic beta cells, mediates glucose uptake and release in hepatocytes.[8] GLUT 4 is present in tissues in which glucose uptake is insulin mediated (e.g., muscle, adipose tissue, cardiac tissue).[8] Under basal conditions, GLUT 4 is normally found mostly in intracellular vesicles.[9] When insulin binds to the insulin receptor on the cell membrane, intracellular signaling pathways are stimulated, causing the GLUT 4–containing vesicles to move to the cell membrane.[9]

Following transport into the cell, glucose is either transformed into pyruvate through the process of glycolysis or stored as glycogen. Glycolysis can provide energy in the form of ATP through aerobic (i.e., pyruvate oxidation to carbon dioxide and water) or anaerobic (i.e., pyruvate conversion to lactate) metabolism. Alternatively, pyruvate can be transaminated to alanine or recycled to glucose via oxaloacetate[10]; these gluconeogenic substrates maintain glucose availability (Figure 2). Lactate metabolism through the Cori cycle provides a constant source of glucose, which is especially important in wounded tissue, leukocytes and erythrocytes, and brain cells[11] (Figure 3). Increased glycolysis occurs when phosphofructokinase, the rate-limiting enzyme for glycolysis, is stimulated by increased cellular uptake of glucose, increased turnover of ATP, and increased AMP production, all of which occur during physiologic stress.[12]

Glycogen is the storage form of glucose. When glucose is taken up by hepatocytes through GLUT-2 receptors, it is converted to glucose-6-phosphate by glucokinase.[5] This is an energy-dependent process requiring ATP. Glucose,
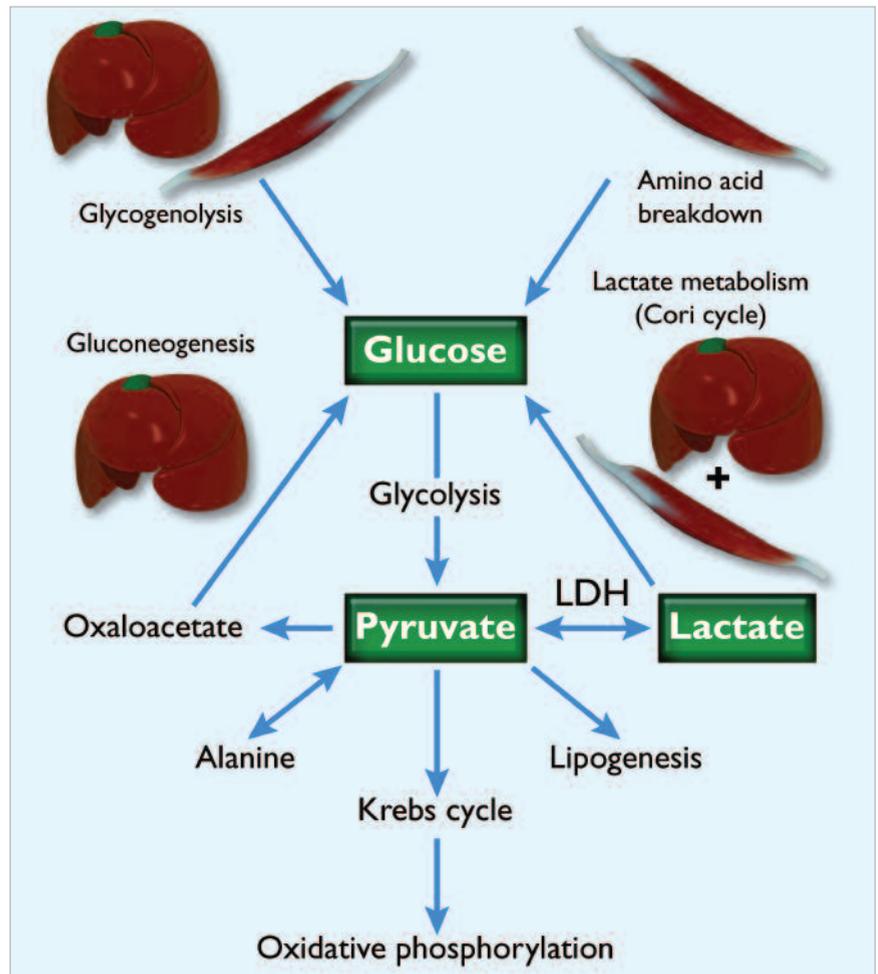


**Figure 1. Glycolysis is the central energy pathway in most living organisms.** Sources of bodily glucose include digestion of carbohydrates, glycogenolysis, gluconeogenesis, amino acid breakdown, and lactate metabolism. Glucose is then converted to pyruvate and enters the Krebs cycle, where oxidative phosphorylation yields energy production. (*LDH* = lactate dehydrogenase)

once phosphorylated, cannot diffuse out of the cell. Glucose-6-phosphate is then converted to glycogen through a series of enzymatic reactions. Glycogenolysis begins when glycogen is degraded into glucose-1-phosphate by phosphorylase and then converted to glucose-6-phosphate. Phosphorylase is activated by epinephrine and glucagon.[5] Glucose phosphatase then splits glucose-6-phosphate into glucose and phosphate. Glucose can then exit the liver cell into systemic circulation (Figure 4).

## GLUCOSE REGULATION

A number of hormones are involved in glucose metabolism and the maintenance of normoglycemia. The blood glucose concentration reflects the balance
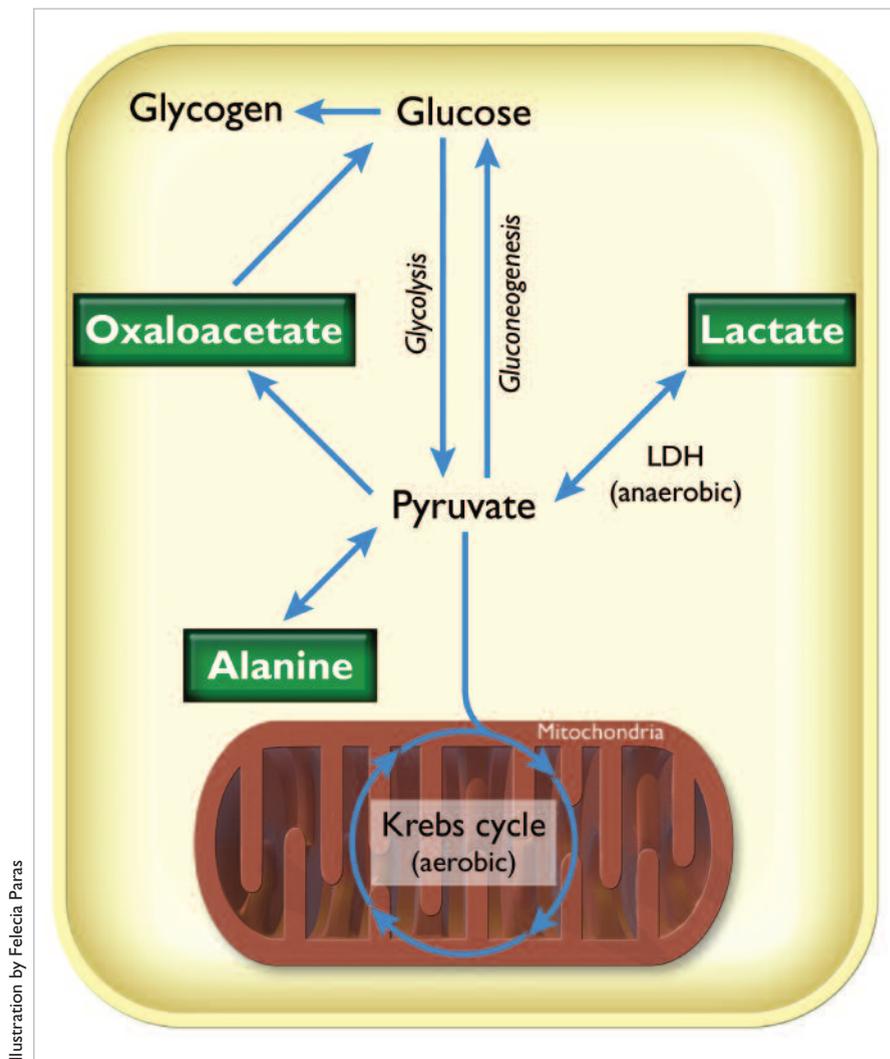
Illustration by Felecia Paras

**Figure 2. The gluconeogenic substrates alanine, lactate, and oxaloacetate maintain glucose availability in the cell.**

between hepatic glucose production and cellular glucose uptake.

In dogs and cats, mild hyperglycemia is defined as a glucose concentration of 130 to 180 mg/dl and severe hyperglycemia as a glucose concentration of greater than 180 mg/dl.[13] When the amount of glucose filtered by the glomerulus exceeds the renal threshold for glucose, glucosuria occurs. The renal transport maximum for glucose is 180 to 220 mg/dl in dogs and 260 to 310 mg/dl in cats.[14] Glucosuria results in osmotic diuresis. Although glucosuria can lower the magnitude of hyperglycemia, it can also result in significant dehydration.

Hyperglycemia can result from increased circulating glucocorticoids, catecholamines, and insulin resistance in criti-cally ill patients. Adrenocorticotropic hormone (ACTH) and thus cortisol lev-els can be increased by multiple mecha-nisms. Following injury, afferent pain pathways to the hypothalamus trigger the release of corticotropin-releasing hor-mone, which stimulates ACTH release from the anterior pituitary.[15] ACTH, in turn, stimulates the adrenal gland to release cortisol from the zonae fasciculata and reticularis.[16] ACTH is also stimu-lated by volume depletion sensed by baroreceptors in the carotid bodies and aortic arch.[16] In addition, catecholamine release is stimulated by decreased blood volume and afferent stimulation of the hypothalamus by pain pathways from the site of injury.[16] The reticular formation and spinal cord transmit signals to post-ganglionic sympathetic nerve endings to release epinephrine and norepinephrine from the adrenal medulla[15] (Figure 5).

The end result of these metabolic processes associated with stress in criti-cally ill patients is an increase in counter-regulatory hormones. This response causes insulin resistance, a clinical state characterized by appropriate levels of insulin but an inability to maintain nor-moglycemia. It is a prominent feature of critical illness and allows hyperglycemia to develop. One mechanism for insulin resistance is a decrease in GLUT-4 activ-ity by cortisol and glucagon.[17] There is also impairment of insulin-stimulated GLUT-4 movement from intracellular vesicles to the plasma membrane despite a normal GLUT-4 concentra-tion.[18,19] This defect may be due to tumor necrosis factor–α (TNF-α) acting in a paracrine fashion[20,21] and increased glucose[22] and/or free fatty acid concentrations.[23] Another mechanism for insulin resistance is decreased activity of the muscular enzymes glycogen synthase[24] and pyruvate dehy-drogenase.[25] These enzymes normally function to convert glucose to glycogen and pyruvate, respectively. When their function is impaired, intracellular glucose concentrations rise, creating an unfavorable concentration gradient for glu-cose uptake into the cells.

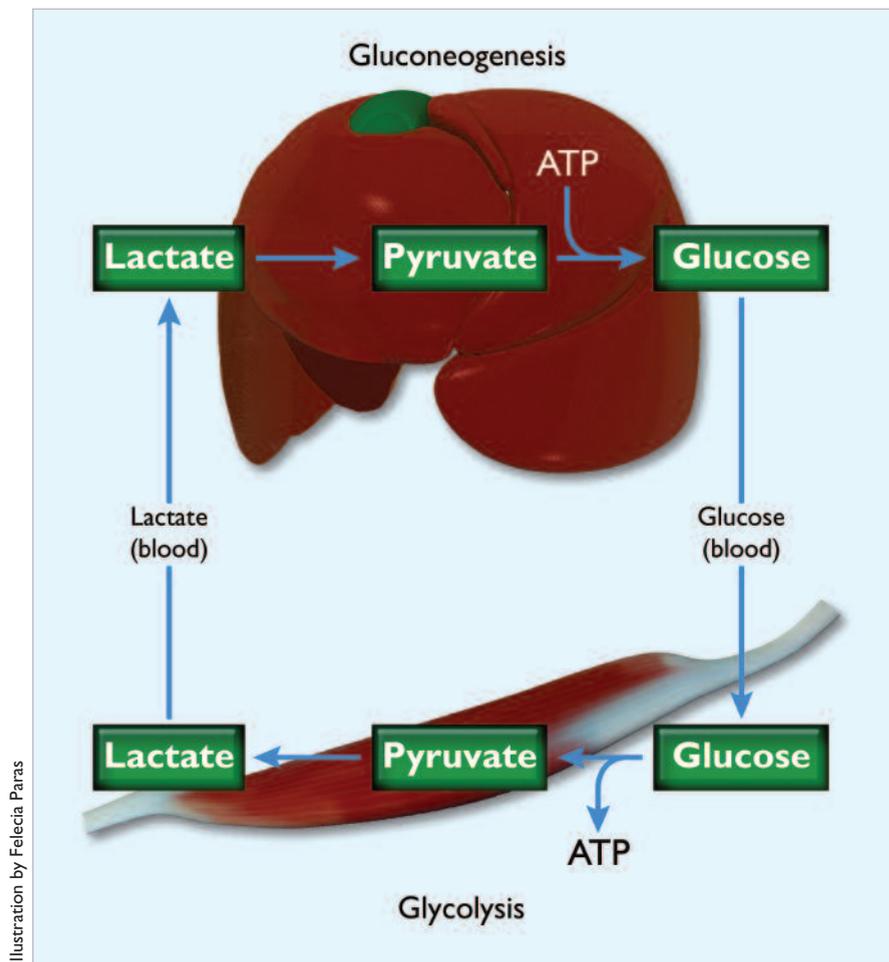Insulin is released in response to hyperglycemia. Insulin promotes fat synthesis and storage, enhances

Illustration by Felecia Paras

**Figure 3. The Cori cycle.** Anaerobic glycolysis can provide short-term energy needs in muscle. The by-product, lactate, diffuses into the blood and is taken up by the liver. The liver uses the enzyme lactate dehydrogenase to convert lactate to pyruvate. Pyruvate is then converted back to glucose via gluconeogenesis.

amino acid transport into cells for protein synthesis and storage, decreases gluconeogenesis, and inhibits proteolysis.[26] Insulin is the primary hormone that stimulates glucose uptake into cells, thus potentially promoting hypoglycemia.

Hypoglycemia is defined as a blood glucose level less than 60 mg/dl. Hypoglycemia can result from increased insulin, increased peripheral glucose uptake, decreased glycogen stores, decreased glycogenolysis, and decreased gluconeogenesis. The counterregulatory hormones (e.g., glucagon, cortisol, growth hormone, catecholamines) are responsible for preventing hypoglycemia (Figure 6). Glucagon is released in response to decreased blood glucose or increased amino acid and cortisol concentrations.[26] Glucagon stimulates liver glycogenolysis and glu-

coneogenesis and, in high concentrations, increases free fatty acid concentrations.[26] Cortisol is released in response to ACTH secretion. Cortisol stimulates gluconeogenesis by mobilizing amino acids into the liver and decreases glucose uptake and use in most cells, particularly myocytes and adipocytes.[16] Cortisol decreases glucose uptake through a number of mechanisms, including decreased number or efficiency of GLUT-4 transporters[17] and increased glucagon and free fatty acid concentrations.[16] Growth hormone reduces glucose uptake in myocytes and adipocytes and stimulates glycogenolysis.[27] In response to severe hypoglycemia, the hypothalamus activates the sympathetic nervous system to release epinephrine and norepinephrine.[26] These catecholamines stimulate $\beta_2$-adrenergic receptors in the liver, resulting in glycogenolysis and increased glucose release.[5] $\alpha$-Adrenergic stimulation of pancreatic beta cells causes decreased insulin release and decreased use of glucose by hepatocytes, myocytes, and adipocytes.[26]

In addition to being caused by the sympathetic and stress responses, hyperglycemia in critically ill patients can be caused by certain medical interventions, such as total parenteral nutrition (TPN), dextrose supplementation, surgery, and administration of glucocorticoids, vasopressors, and anesthesia (see box on page 365). In one study[28] of critically ill humans, elevated glucose levels caused by TPN were associated with an increased risk for cardiac complications, infection, sepsis, acute renal failure, and death. The relationship between elevated blood glucose levels and adverse outcomes suggests that tight glycemic control might benefit these patients. In a retrospective study[29] of cats and dogs receiving TPN, 30% of patients became hyperglycemic. In cats, hyperglycemia 24 hours after initiation of TPN has been associated with a poor prognosis.[30] In contrast, in a retrospective study[31] of cats and dogs that received partial parenteral nutrition, 15% became hyperglycemic, but this had no effect on the morbidity and mortality rates.

Anesthesia and surgery both modulate normal metabolic function.[32–36] Anesthetic drugs known to cause transient hyperglycemia include ketamine, $\alpha_2$-agonists, and opioids. Ketamine stimulates epinephrine release.[33] $\alpha_2$-Adrenergic agonists, xylazine,[34] and medetomidine[35] can cause hyperglycemia by binding to $\alpha_2$-adrenergic receptors on pancreatic beta cells and thereby inhibiting insulin release. Morphine stimulates the release of growth hormone and ACTH,[36] thereby promoting hyperglycemia.

Hyperglycemia is common in people[1,37] and animals[38] in the early stages of sepsis. Studies[24,39,40] have found conflicting results on whether this is due to decreased glucose oxidation during sepsis or to increased glucose production. Hepatic glucose production is significantly increased.[41] Current evidence suggests that overall glucose uptake is also increased but insulin-mediated glucose uptake by skeletal and adipose tissue is decreased[24] and glucose uptake by the reticuloendothelial system and leukocytes is increased.[39,40]

Critically ill patients are in a catabolic state in which the increased demand for energy substrates is met by degrading endogenous sources of glycogen. This state is characterized by hyperglycemia, hyperlactatemia, and increased oxygen demand.[10] In the past, this catabolic state was believed to be beneficial by providing extra energy substrates to glucose-dependent tissues (i.e., the brain, erythrocytes, leukocytes).[10] Evidence now suggests that hyperglycemia produced during critical illness can have various detrimental effects on patients.

## POTENTIAL DETRIMENTAL EFFECTS OF HYPERGLYCEMIA

Research into the mechanisms that cause the detrimental effects of hyperglycemia has mainly focused on modulation of inflammation, changes in vascular tone, and alteration of coagulation (see box on page 369). The effects of hyperglycemia on the heart, brain, and endothelium have been the most researched.

### Inflammation

Unfortunately, most studies that have evaluated the mechanisms of inflammatory response modulation under hyperglycemic conditions have been conducted in laboratory animal models and in humans with diabetes and do not necessarily represent events in critical illness. However, it has been well documented that humans with diabetes have a decreased ability to fight infection.[42,43]

### Causes of Hyperglycemia in Critically Ill Patients

- Increased catecholamines (endogenous or exogenous)
- Increased glucocorticoids (endogenous or exogenous)
- Insulin resistance
- TPN
- Dextrose infusion
- Surgery
- Anesthesia
- Inflammatory mediators

Based on studies in laboratory animals and humans with diabetes, inflammation is increased but essential function of the inflammatory response is impaired by hyperglycemia. Both migration and phagocytic ability of polymorphonuclear cells are hampered,[44,45] leading to an increased risk for bacterial proliferation. Another aspect of hyperglycemia-associated immune impairment may be related to nonenzymatic glycosylation of immunoglobulins, which causes their inactivation, contributing to an increased risk for infection.[46,47] As in many inflammatory responses, hyperglycemia induces nuclear factor $\kappa\beta$ (NF-$\kappa\beta$), a transcription factor that increases production of cytokines, particularly TNF-$\alpha$, interleukin-1$\beta$, and interleukin-6.[48–50] Production of complement, a family of serum proteins critical in bacterial killing and inflammation, is increased, but its function is impaired.[45,46,51,52] Hyperglycemia causes increased interactions among endothelial cells, monocytes, lymphocytes, and neutrophils through induction of adhesion molecules.[45] Hyperglycemia also results in increased expression of protein kinase C$_{\alpha\beta o}$. These intracellular messengers activate NF-$\kappa\beta$, thereby increasing adhesion molecule expression and inhibiting complement- and immunoglobulin-mediated phagocytosis.[45,51]

### Coagulation and Endothelium

Research[53] has demonstrated an important relationship between inflammation and coagulation. Hyperglycemia stimulates not only inflammation but also coagulation. Procoagulant effects of hyperglycemia include activation of the tissue factor pathway,[54] inhibition of proteins C[55] and S,[48] increase in blood levels of clotting factors,[56,57] platelet activation,[58,59] and inhibition of the fibrinolytic system.[57] Hyperglycemia also stimulates interleukin-6, an inflammatory cytokine with procoagulant effects.[48]

In addition to promoting inflammation and coagulation, hyperglycemia interferes with normal endothelial function.[60–62] Local activation of the endothelium is neces-
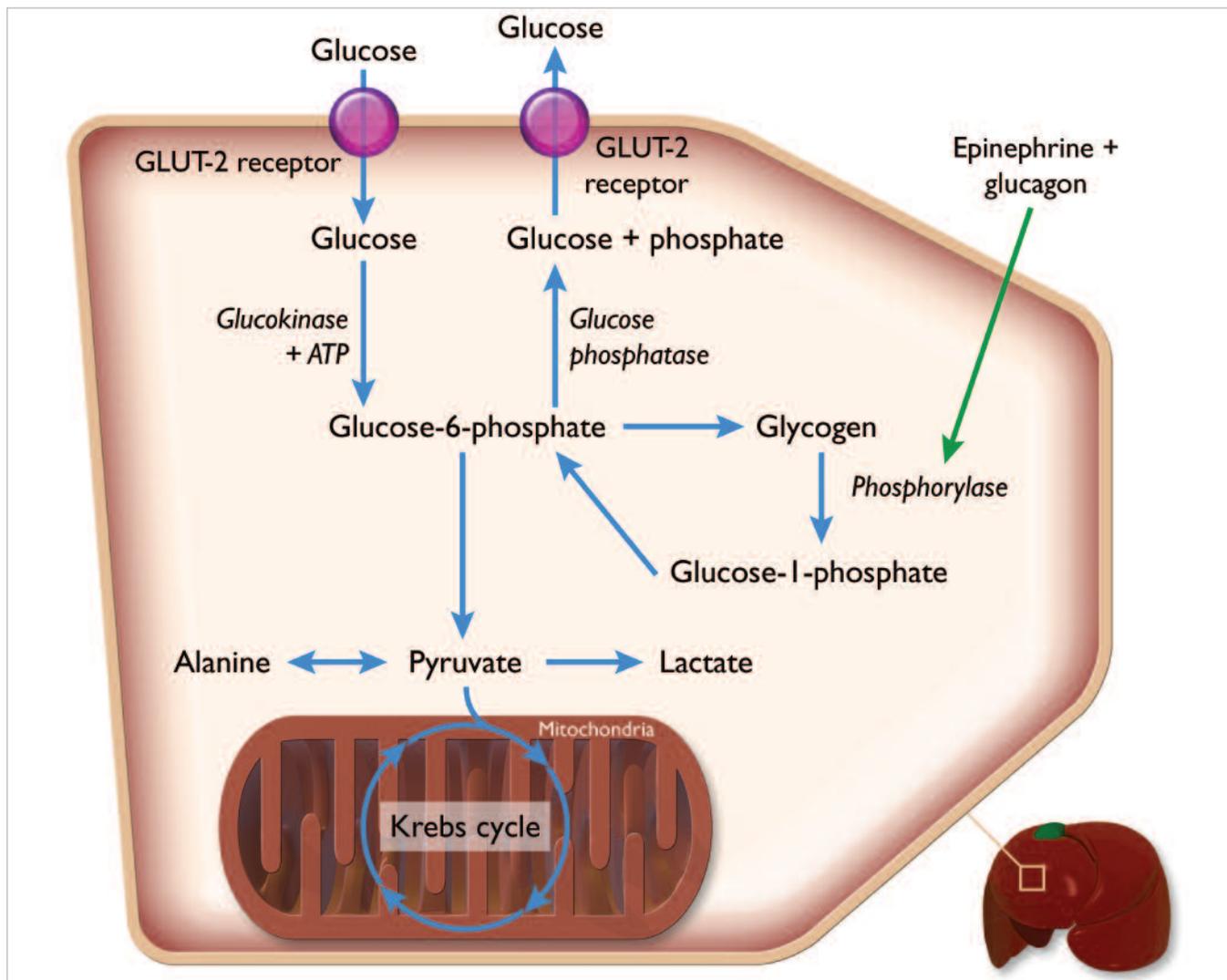
**Figure 4. Glucose taken up by the liver is phosphorylated into glucose-6-phosphate and cannot diffuse from the cell.** Glucose-6-phosphate can be transformed into pyruvate for entry into the Krebs cycle or into glycogen for storage. Glycogen breakdown is stimulated by epinephrine and/or glucagon.

sary for the migration and adhesion of leukocytes to the site of inflammation. Hyperglycemia activates the endothelium.[60] Studies[61,62] have attempted to determine how hyperglycemia is detrimental to the endothelium. Whether hyperglycemia results in vasoconstriction or vasodilation varies, depending on the tissue studied and the amounts and types of mediators and receptors involved.

**Cardiac Effects**

In humans or animal models with cardiac disease, hyperglycemia has been found to cause detrimental effects via increased inflammation, vasoconstriction, and elevated free fatty acid concentration.[63] Increased free

fatty acids can be cytotoxic to the myocardium.[63] In human studies of congestive heart failure, the mechanisms of hyperglycemia include reduced insulin-mediated glucose uptake,[64] impaired insulin signal transduction, and antagonism at insulin receptors.[65]

**Traumatic Brain Injury**

Numerous mechanisms have been proposed to explain the relationship between hyperglycemia and enhanced damage in patients with traumatic, hypoxic, or ischemic brain injury.[66–70] Current opinions differ as to whether hyperglycemia simply reflects more severe injury or truly causes direct harm to brain-injured patients.[71–73]

During hypoxemia or ischemia, the brain develops lactic acidosis as end products of anaerobic metabolism accumulate. Hyperglycemia allows more anaerobic metabolism to occur and more by-products to accumulate. Lactic acid is cytotoxic to neuronal and glial cells.[66] Glial cells produce myelin to protect neurons. Hyperglycemia in patients with traumatic brain injury is associated with increases in free radical production,[67] excitatory amino acid release,[68] cerebral edema,[69] and cerebral vasoconstriction.[70]

Human clinical studies[71–73] have shown a relationship between hyperglycemia and a worse outcome in brain-injured patients. Studies[68,74] have also demonstrated that hyperglycemia worsens secondary brain injury in laboratory animal models of ischemia and hemorrhage associated with traumatic brain injury.

## PROGNOSIS

In the veterinary literature, there is little research relating serum glucose to outcome in clinical patients. Few studies[32,75–77] have attempted to correlate glucose levels with outcome in specific conditions (e.g., head trauma, congestive heart failure, sepsis).

One clinical retrospective veterinary study[78] of head trauma in dogs and cats found an association between hyperglycemia and severity of injury but not outcome. A few studies have investigated hyperglycemia in veterinary cardiac patients. Brady et al[75] reported higher glucose levels associated with worse outcome (median glucose levels: 101 mg/dl in survivors and 120 mg/dl in nonsurvivors). Freeman et al[76] found elevated glucose and TNF-α levels in dogs with congestive heart failure, but TNF-α levels did not directly correlate with the level of hyperglycemia found. In a study[32] that compared the glucose levels of septic and nonseptic dogs and cats before and after surgery, there was a trend toward higher mortality rates with severe postsurgical hyperglycemia in cats and dogs with sepsis compared with those with mild postsurgical
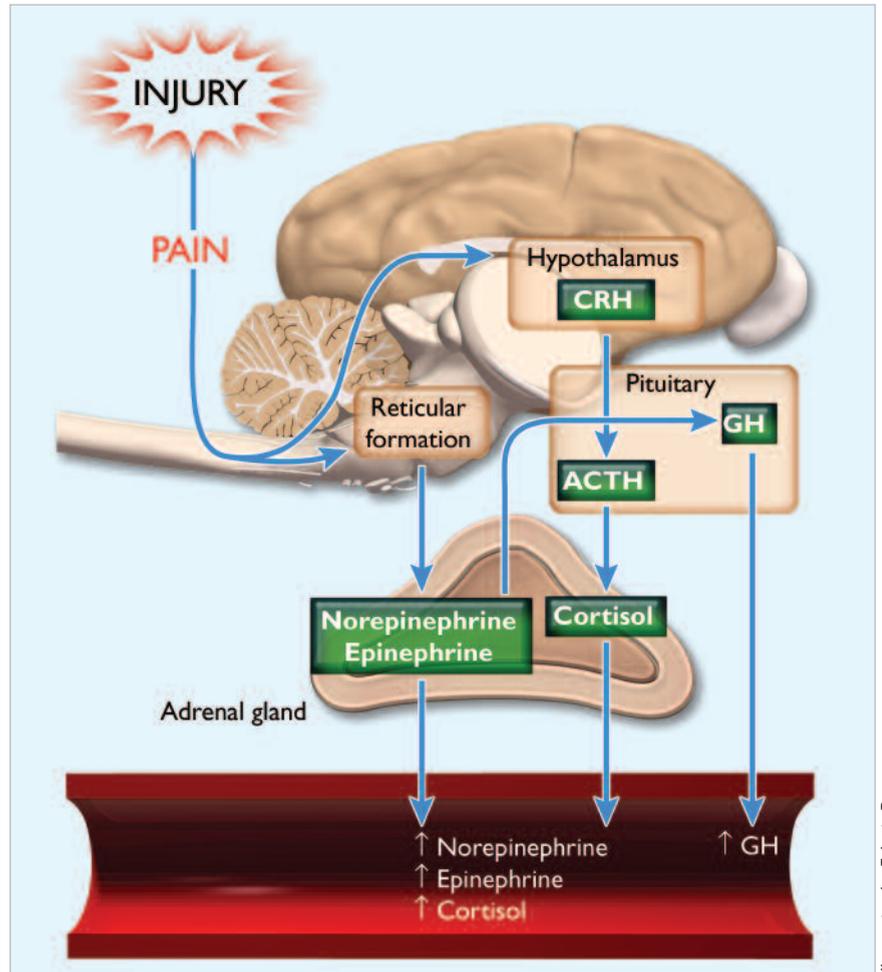


**Figure 5. Metabolic stress processes associated with resultant hyperglycemia.** Stimulation of afferent pain pathways and blood volume depletion cause increased cortisol and catecholamine (primarily epinephrine and norepinephrine) production by the adrenal glands. Cortisol stimulates gluconeogenesis and decreases glucose uptake in adipocytes and myocytes. Catecholamines stimulate the release of growth hormone (GH), which also reduces glucose uptake in myocytes and adipocytes while stimulating glycogenolysis. (*ACTH* = adrenocorticotropic hormone; *CRH* = corticotropin-releasing hormone)

hyperglycemia. These findings did not reach clinical significance. Meaningful clinical studies to relate hyperglycemia with outcome are difficult to conduct in animals because of the wide spectrum of disease severity and the many interventions that can affect glucose levels.

## INTENSIVE INSULIN THERAPY FOR GLYCEMIC CONTROL

Recent clinical studies[1–4,50,77] in humans have shown decreased mortality rates with strict glycemic control using insulin therapy not only in patients with diabetes
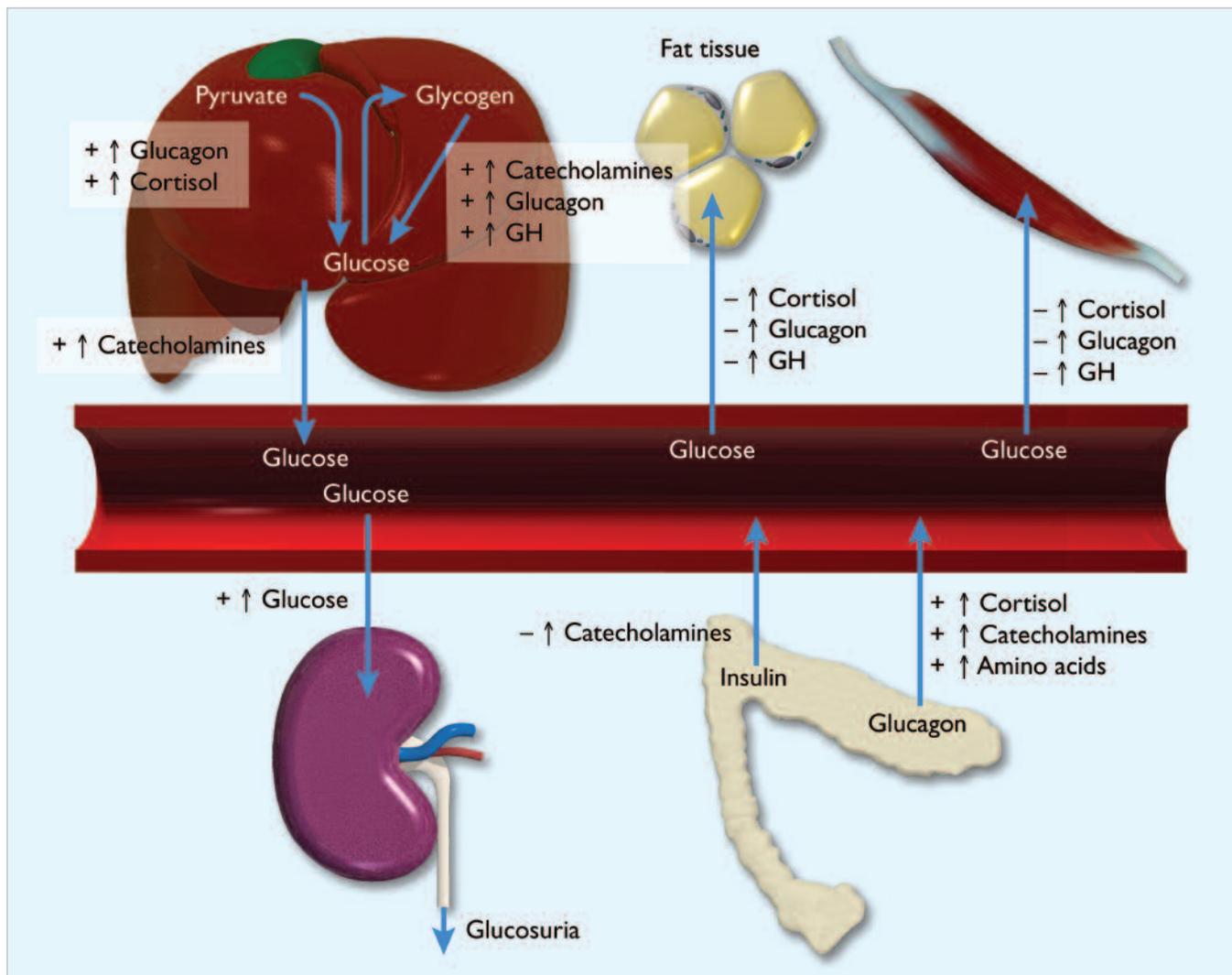
**Figure 6. Effects of counterregulatory hormones on glucose regulation.** *Liver:* Glycogenolysis is stimulated by catecholamines, glucagon, and growth hormone. Gluconeogenesis is stimulated by glucagon and cortisol. Catecholamines cause increased release of glucose from hepatocytes. *Adipose and muscle tissue:* Increased cortisol, glucagon, or growth hormone levels decrease glucose uptake. *Pancreas:* Increased cortisol, catecholamine, or amino acid levels stimulate glucagon release. Increased catecholamine levels inhibit insulin release.

but also in patients with hyperglycemia that was associated with critical illness. Maintenance of normoglycemia using insulin therapy decreased not only the mortality rate but also the rates of acute renal failure, ventilatory support, transfusions, polyneuropathy, and infections.[1] Several clinical cardiac studies[79–81] have shown improved outcome and decreased complications with glycemic control in both diabetic and nondiabetic patients. In a recent human clinical trial[82] in a surgical intensive care unit, a subpopulation with isolated traumatic brain injury had a reduced risk for prolonged mechanical ventilation, had decreased intracranial pressure, and maintained cere-

bral perfusion pressure with an eight-fold lower dose of vasopressors through strict glycemic control. No other published human clinical trials have demonstrated improved outcome when glucose has been strictly controlled in hyperglycemic patients with traumatic brain injury. A rabbit model of traumatic burn injury found that using insulin to maintain normoglycemia prevented much of the weight loss, lactic acidosis, and monocyte dysfunction that occurred in the hyperglycemic group.[83] Whether the maintenance of normoglycemia or the use of insulin is responsible for the beneficial effects in clinical trials remains under investigation.[79]

## TREATMENT

Insulin has several antiinflammatory effects.[84,85] Insulin suppresses the generation of numerous inflammatory mediators, including TNF-α,[86,87] macrophage migration inhibitory factor,[88] superoxide anions,[89] and NF-κβ.[84]

The primary approach to maintenance of glycemic control in critically ill patients is intensive insulin therapy. To date, attempts at hypocaloric nutrition as a means of decreasing hyperglycemia do not appear beneficial.[90] It is important to remember that numerous drugs, such as glucocorticoids, catecholamines, and certain anesthetics (ketamine, α₂-agonists, morphine),[33–36] as well as supplements, such as dextrose and TPN,[28–31] may exacerbate hyperglycemia. Avoiding or limiting the use of these treatments may be indicated in certain situations to prevent hyperglycemia.

The use of insulin therapy to provide strict glycemic control in critically ill animals has been reported only in animals with diabetic ketoacidosis.[91] In these patients, a constant-rate infusion of regular insulin was shown to gradually reduce hyperglycemia and ketogenesis over a period of 10 to 24 hours.[91] In diabetic animals, regular insulin is usually administered at a dose of 1 to 2 U/kg/day (0.04 to 0.08 U/kg/hr) mixed in 250 ml of saline at a rate of 10 ml/hr. Although the routine use of insulin therapy in critically ill hyperglycemic veterinary patients cannot currently be recommended, a modified protocol can be used to provide strict glycemic control in select nondiabetic hyperglycemic patients with head trauma or sepsis: a lower dose of insulin (0.25 to 1 U/kg/day) is used, and the infusion rate is decreased by 50% to 75% when the glucose level drops below 150 mg/dl. Blood glucose levels must be monitored frequently to prevent hypoglycemia. Ideally, the constant-rate infusion should be adjusted to maintain a blood glucose concentration of 85 to 130 mg/dl. The insulin should be discontinued when the blood glucose level drops below 85 mg/dl. Animals receiving insulin therapy are prone to hypoglycemia, hypokalemia, hypophosphatemia, and hypomagnesemia.[92] Hypoglycemia can result in seizures, coma, and death.[13] Hypokalemia and hypomagnesemia cause muscular weakness and cardiac arrhythmias.[13] Hypophosphatemia causes muscular weakness and hemolysis.[13] Adequate nutrition should be provided to prevent hypoglycemia, and intravenous fluids should be supplemented with potassium, phosphorus, or magnesium, as needed. Interventions that can cause hyperglycemia, such as TPN infusions, should be avoided in critically ill patients with head trauma or cardiovascular disease.

### Changes Associated with Hyperglycemia in Humans and Laboratory Animal Models

**Immune system modulation**
- Activation of adhesion molecules (increased interaction of endothelial cells, neutrophils, monocytes, platelets)
- Increased cytokine production
- Increased complement production
- Decreased complement function
- Decreased polymorphonuclear cell migration
- Decreased phagocytosis by polymorphonuclear cells
- Glycosylation of immunoglobulin

**Endothelial dysfunction**
- Vasodilation (increased nitric oxide)
- Vasoconstriction (decreased nitric oxide)

**Coagulation**
- Activation of tissue factor pathway and platelets
- Inhibition of proteins C and S and fibrinolysis
- Increased levels of clotting factors

**Cardiac**
- Increased free fatty acids
- Vasoconstriction

**Traumatic brain injury**
- Lactic acidosis
- Increased free radical production
- Increased excitatory amino acid release
- Cerebral edema
- Cerebral vasoconstriction

**Other**
- Dehydration secondary to osmotic diuresis

## CONCLUSION

Maintenance of normal blood glucose concentrations is important for normal cellular function. Persistent hyperglycemia indicates a significant loss of one or more major homeostatic mechanisms. It may indicate increased hepatic glucose production, insulin resistance, or decreased cellular uptake of glucose. In humans and animal models, persistent increased blood glucose has been shown to have numerous detrimental effects, including increased inflammation, immune system dysfunction, stimulation of coagulation, and modulation of the endothelium. In critical illness, hyperglycemia can theoretically have detrimental effects on many different organs, particularly the brain, heart, and endothelium.

Many mechanisms for hyperglycemia have been explored in laboratory animal models and humans with diabetes. In critical illness, not all of these models necessarily apply. There may be major differences in the

## Key Points

- A reduced mortality rate with the use of intensive insulin therapy for glycemic control in critically ill humans does not necessarily imply the same results for cats and dogs. Further research is warranted to determine the incidence of hyperglycemia in various subgroups of critically ill animals and whether strict glycemic control is indicated to reduce morbidity and mortality rates.

- If not adequately monitored, administration of insulin can cause devastating hypoglycemia, hypokalemia, hypophosphatemia, or hypomagnesemia in critically ill patients.

- Hyperglycemia interferes with normal endothelial function and coagulation as well as inflammation. The end changes to endothelial function vary, depending on the tissue being studied and the levels of specific mediators and receptors involved.

metabolic mechanisms of disease between critically ill humans and cats or dogs. A reduced mortality rate with the use of intensive insulin therapy for glycemic control in critically ill humans does not necessarily imply the same results for cats and dogs. Further research is warranted to determine the incidence of hyperglycemia in various subgroups of critically ill animals and whether strict glycemic control is indicated to reduce morbidity and mortality rates. Although the risk:benefit ratio of active interventions, such as intensive insulin therapy to maintain glycemic control, has not been evaluated in animals, management strategies to avoid hyperglycemia, when possible, are likely indicated. However, until prospective clinical studies have been conducted in critically ill cats and dogs, intensive insulin therapy should be used cautiously and only with intensive monitoring.

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## ARTICLE #2 CE TEST

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**1. Glucose is transported into cells by**
   a. passive diffusion.
   b. solute drag.
   c. active transport and facilitated diffusion.
   d. sodium–glucose antiporter.

**2. Glucagon release is stimulated by**
   a. a decreased cortisol level.
   b. a decreased level of circulating amino acids.
   c. hypoglycemia.
   d. a decreased insulin level.

**3. In critical illness, hyperglycemia can be caused by**
   a. the stress response, which induces glucocorticoid release.
   b. catecholamine release.
   c. anesthesia or surgery.
   d. all of the above

**4. In critically ill patients, administration of insulin can result in**
   a. hyperkalemia.
   b. hypokalemia.
   c. glucosuria.
   d. increased free fatty acid release.

**5. The carrier protein that requires insulin to mediate glucose transport is**
   a. GLUT 1.
   b. sodium–glucose cotransporter.
   c. GLUT 4.
   d. albumin.

**6. Insulin stimulates glucose uptake in**
   a. hepatocytes.          c. adipocytes.
   b. myocytes.             d. all of the above

**7. In a laboratory animal model, the group that received insulin to maintain normoglycemia after a severe burn injury _____ compared with the control (hyperglycemic) group.**
   a. had a better survival rate
   b. had an increased incidence of lactic acidosis
   c. lost less weight
   d. had decreased immune function

**8. In patients with congestive heart failure, hyperglycemia develops secondary to**
   a. impaired insulin-signal transduction.
   b. increased insulin-mediated glucose uptake.
   c. increased insulin-receptor activity.
   d. increased glucagon release.

**9. Which statement regarding hyperglycemia is incorrect?**
   a. It can stimulate cytokine production.
   b. It increases adhesion molecule activation.
   c. It results in glycosylation of immunoglobulins.
   d. It improves phagocytosis by polymorphonuclear cells.

**10. In the veterinary literature, hyperglycemia has been associated with**
   a. decreased survival in patients with head trauma.
   b. increased TNF-$\alpha$ levels in patients with congestive heart failure.
   c. a poor prognosis in cats receiving TPN.
   d. increased survival in surgical patients with sepsis.