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Blood Glucose Management During Critical Illness

Barry A. Mizock
Division of Critical Care Medicine, Department of Medicine, Cook County Hospital, Chicago, IL, USA

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Introduction

The term "stress hyperglycemia" is used to describe an altered metabolic state induced by acute illness characterized by transient elevations in blood glucose in individuals who lack a previous history of diabetes [1]. Many patients regain normal glycemic status once the acute illness resolves; however, stress hyperglycemia may also be a harbinger of subsequent diabetes. Husband et al. studied patients not known to have diabetes who were hyperglycemic following admission for suspected acute myocardial infarction; 63% had glucose tolerance tests consistent with diabetes two months later [2].

The reported incidence of stress hyperglycemia in hospitalized patients varies due to inconsistencies in criteria used to define the condition; blood glucose concentrations ranging from 6.7 to 11.2 mmol/L have been proposed by various authors [1]. Determination of the true incidence of stress hyperglycemia is further obscured by the fact that some studies included patients with preexisting diabetes mellitus. The reported prevalence of stress hyperglycemia also varies based on the severity of illness in the patient population surveyed; one study of critically-ill patients with sepsis or severe trauma reported an incidence of stress hyperglycemia of approximately 50% [3].

The presence of a hyperglycemic milieu during critical illness is associated with a number of adverse consequences such as: increased incidence of wound infections post-operatively, and worsened outcome in head injury, stroke, and myocardial infarction [4–6]. A recent study examined the hospital records of approximately 2000 adult patients; hyperglycemia was present in 38% of patients admitted to the hospital; of these, 1/3 had no previous history of diabetes. Patients with newly discovered hyperglycemia were found to have a higher in-hospital mortality (16%) when compared to those patients who were known to be diabetic (3%), or to those who were normoglycemic (1.7%). The group with newly discovered hyperglycemia also had an increased duration of hospitalization, were more likely to be admitted to the ICU, and had a greater probability of requiring nursing home care at discharge [7].

Aggressive treatment of hyperglycemia in diabetics who are postoperative or who are critically ill has been shown to be beneficial by reducing infectious risk. In contrast, there is a paucity of data supporting tight control in patients with stress hyperglycemia, and many clinicians ignore modest elevations in blood glucose in this population.

This article will review the pathophysiology of hyperglycemia during acute illness, examine data that demonstrate benefits of tight glycemic control, and describe an approach to management of this condition.

Pathophysiology of Stress Hyperglycemia

The stress response to critical illness

The initial description of the metabolic alterations induced by critical illness is attributed to Sir David Cuthbertson who in 1942 categorized the hypometabolic ("ebb") and hypermetabolic ("flow") phases following severe traumatic injury [8]. The *ebb phase* begins immediately after injury and typically lasts 12–24 hours. It is associated with decreased peripheral perfusion and a reduction in energy expenditure. Hyperglycemia during the ebb phase results from hepatic glycogenolysis consequent to catecholamine release and direct sympathetic stimulation of glycogen breakdown. The *flow phase* is initiated by restoration of systemic oxygen delivery and metabolic substrate. Hyperglycemia during the flow phase results from increased hepatic glucose production as well as insulin resistance in skeletal muscle. The flow phase typically lasts 10–14 days and merges into an anabolic phase over the next few weeks.

The stress response to critical illness represents a complex interaction between the neuroendocrine and cytokine systems [9]. The stress response is coordinated by corticotropin-releasing hormone (CRH) and

Corresponding author: Barry A. Mizock.
E-mail: bmizock@earthlink.net

locus caeruleus norepinephrinergic neurons of the hypothalamus and brain stem. These areas regulate the hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system respectively. CRH promotes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn increases release of cortisol by the adrenal cortex. Cytokines have also been shown to play an important role in the stress response; the term "immune-hypothalamic-pituitary-adrenal axis" has been proposed to emphasize the important role of cytokines in the regulation of the HPA [10]. Tumor necrosis factor (TNF), interleukin-1, and interleukin-6 stimulate the HPA by promoting the release of CRH and ACTH [11–13]. Cytokines also act directly on the adrenal cortex to increase glucocorticoid synthesis [9].

Stress-induced alterations in carbohydrate metabolism

Several alterations in carbohydrate metabolism contribute to the development of stress hyperglycemia. They include: increased glucose production, diminished peripheral glucose utilization, and insulin resistance [1]. Most forms of acute critical illness are associated with an elevated rate of hepatic glucose production, typically more than two standard deviations above normal [1,14]. The key pathways that determine hepatic glucose production are gluconeogenesis (GNG) and glycogenolysis. Lactate and alanine are the major substrates for GNG during stress; hepatic lactate extraction is augmented 2–3 fold during hypermetabolic sepsis [15]. The major sources of lactate during stress are tissue macrophages and infiltrating neutrophils in lung, the gastrointestinal tract, and wound [16–19]. These cells produce lactate as the result of enhanced glycolytic flux consequent to increased phagocytic activity [19]. The liver may also be an organ of lactate production, particularly in patients who have acute or chronic hepatic dysfunction [20]. Lactate is converted to glucose in the Cori cycle, whereas alanine released by skeletal muscle is reconstituted to glucose via the glucose-alanine cycle [1]. Glycerol may also be a significant precursor for GNG during critical illness [21]. Glucagon is the primary hormonal stimulator of GNG during the flow phase, with catecholamines playing a smaller role [1]. Patients with hypermetabolic stress (e.g., burns, sepsis, trauma) demonstrate a significant increase in glucagon in the blood [14]. However, the ability of glucagon to stimulate GNG appears to be transient; sustained stimulation requires the participation of epinephrine, cortisol and growth hormone [22,23]. Cytokines (e.g., TNF) increase hepatic GNG during stress by stimulating glucagon secretion [24]. The kidneys also produce glucose through GNG; glutamine is the major gluconeogenic precursor and epinephrine is the primary stimulator of renal GNG (glucagon does not appear to enhance renal GNG) [25]. McGuiness et al. infused a mixture of stress hormones to dogs and elicited a significant increase in renal glucose output [26]. However, the role of the kidneys in the pathogenesis of stress hyperglycemia in humans has not been well studied.

Insulin resistance is seen in many forms of critical illness; this process appears to be most prominent during sepsis [14,27]. The degree of insulin resistance appears to be directly proportional to the severity of the stress response [28]. Insulin resistance is categorized as central or peripheral. *Central insulin resistance* refers to a decreased effect of physiologic concentrations of insulin to suppress hepatic glucose production, whereas *peripheral insulin resistance* refers to a diminished ability of insulin to promote glucose uptake in insulin-sensitive tissues (e.g., muscle, fat). Recent data have suggested that the pathogenesis of central insulin resistance may involve acquired defects in the activity of certain hepatic enzymes (e.g., glucokinase) (see below) [29]. The mechanism for peripheral insulin resistance was initially attributed to decreased oxidative glucose utilization in skeletal muscle secondary to downregulation of pyruvate dehydrogenase [30]. However, this mechanism was brought into question by data obtained during burn that demonstrated an increase in peripheral oxidation of pyruvate [31,32]. The most current hypothesis of stress-induced peripheral insulin resistance implicates decreased non-oxidative glucose utilization in skeletal muscle consequent to decreased glycogen synthesis [27,33]. This metabolic alteration may be mediated by cytokine and/or hormone-induced alterations in the signaling pathways that regulate glycogen synthase activity [34]. Shangraw et al. compared insulin resistance in septic and nonseptic patients with burn in order to test if the maximal biological effectiveness of insulin is altered [27]. They found that pharmacologic doses of insulin were effective in suppressing hepatic glucose production in both septic and nonseptic burn patients; however, peripheral glucose uptake in septic, but not nonseptic burn injury, was refractory to pharmacologic insulin stimulation [27].

Hepatic autoregulation of glucose production

It has been observed that certain non-hormonal mechanisms regulate hepatic glucose production. Several studies have demonstrated that when GNG is stimulated by increasing the concentration of gluconeogenic precursors, hepatic glucose production is unchanged [35,36]. This process has been termed "*hepatic autoregulation*"; it appears to be mediated in part by alterations in the activity of the *glucose cycle* [29,37]. In this pathway, the enzymes glucokinase and glucose-6-phosphatase promote apparently futile cycling between glucose and glucose-6-phosphate [1,37] (Fig. 1). In reality, this cycle is not truly futile but rather represents an important process by which

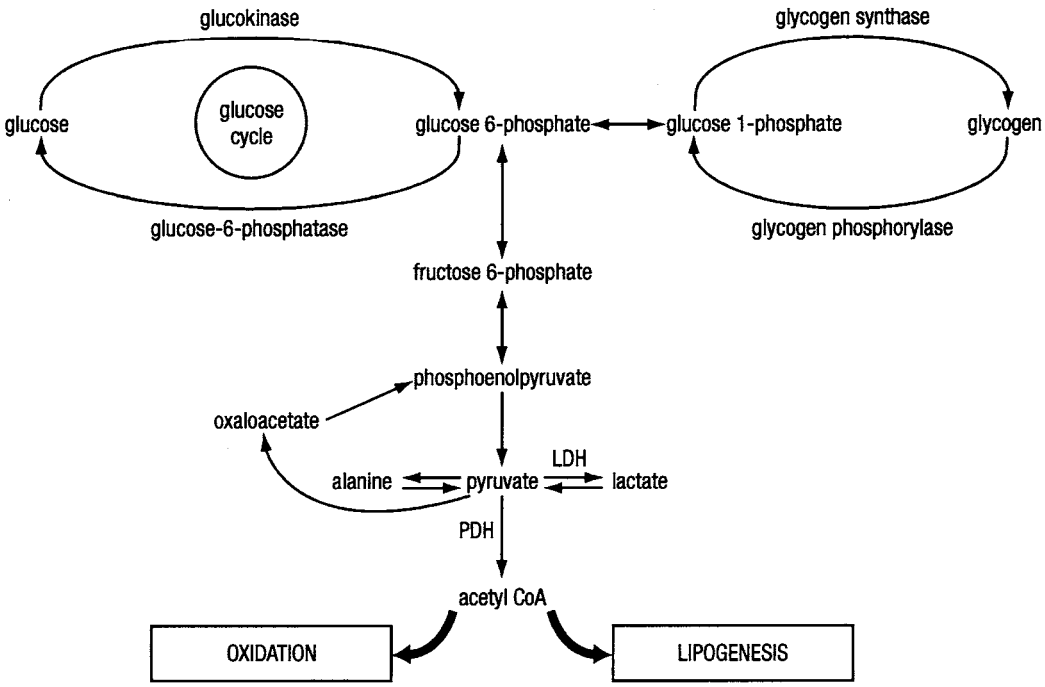

Fig. 1. *Overview of carbohydrate metabolism. PDH = pyruvate dehydrogenase; LDH = lactate dehydrogenase.*

the moment-to-moment homeostasis of hepatic glucose production is maintained [1,29]. It has been postulated that stress-induced changes in the activity of glucokinase lead to an alteration of the autoregulatory process than in turn promotes hyperglycemia [29]. An acquired change in the activity of glucokinase has also been implicated as playing a role in enhanced glucose production observed in patients with type II diabetes [38].

Other Causes of Hyperglycemia During Stress

Other conditions promoting hyperglycemia during critical illness include: cirrhosis (hepatic fibrosis impairs glycogen storage), pancreatitis, drugs (e.g., corticosteroids, thiazide diuretics, protease inhibitors, pentamidine, phenytoin, phenothiazines), total parenteral nutrition (TPN) (see below), hypokalemia (impairs insulin secretion), chromium deficiency (required for synthesis of glucose tolerance factor), bed rest and advanced age [1].

Adverse Effects of Hyperglycemia

Hyperglycemia promotes an osmotic diuresis with hypovolemia and electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypophosphatemia). The associated increase in serum tonicity results in intracellular dehydration in brain that can lead to coma. Hyperglycemia may also worsen catabolism in skeletal muscle [39].

Immune function is adversely affected by hyperglycemia. In this regard, a variety of immune defects have been reported in association with increased blood glucose concentration such as inhibition of cytokine release from macrophages, impaired phagocytosis and free-radical production [40]. Zerr et al. found that diabetics undergoing open heart surgery have a greater risk of deep wound infections (1.7%) when compared to a non-diabetic population (0.4%) [4]. Similarly Pomposelli et al. observed that diabetic patients undergoing major cardiovascular or abdominal surgery were found to have an increased risk of infection that was further exacerbated by early postoperative hyperglycemia [41]. In addition to diabetics, patients with stress hyperglycemia also appear to be at increased risk of infection [7,40].

Hyperglycemia worsens the prognosis in patients with stroke or head injury [6,7]. However, it is not clear whether the observed increase in mortality is due to a direct toxic effect of hyperglycemia on brain or whether hyperglycemia reflects a greater severity of stress. Woo et al. measured blood glucose, glycosylated hemoglobin, and fructosamine in patients admitted with acute stroke [42]. Based on these results and historical features, the patients were divided into known diabetics, newly diagnosed diabetics, stress hyperglycemia and nondiabetics. Although patients with diabetes had similar glucose concentrations to those with stress hyperglycemia, their outcome was not worse; the prognosis seemed to be more related to severity of disease rather than a direct adverse effect of

hyperglycemia on brain [42]. Until studies are available that clearly demonstrate benefit of normalization of blood glucose on outcome in acute stroke and head injury, the association between hyperglycemia and increased mortality in these conditions should probably be considered an epiphenomenon.

Benefits of Tight Glucose Control During Stress

A number of studies have observed clinical benefit of tight glycemic control in diabetics who are postoperative or critically ill. Rassias et al. in a study of diabetic patients undergoing cardiac surgery, found improved neutrophil phagocytic activity in those who had tight glucose control (glucose maintained below 11.1 mmol/L [<200 mg/dl]) intraoperatively using an insulin infusion, relative to those patients who received usual management [43]. Zerr et al. demonstrated that aggressive control of blood glucose to maintain mean blood glucose level less than 11.1 mmol/L following cardiac surgery in diabetics reduced the incidence of deep sternal infection relative to standard therapy [4]. Malmberg et al. found that diabetic patients with acute myocardial infarction who were treated with an insulin-glucose infusion targeted to a blood glucose of 7–10.9 mmol/L (125–196 mg/dl) had a 29% reduction in relative mortality at 1 year compared to patients receiving conventional therapy [44]. Van den Berghe et al., attempted to further delineate the potential benefits of tight glycemic control by "pushing the therapeutic envelope" [45]. Postoperative ICU patients were randomized to either standard control (blood glucose maintained <11.1 mmol/L [<200 mg/dl]) or normoglycemia (blood glucose maintained between 4.4–6.1mol/L [80–110 mg/dl]). Approximately 1500 patients were entered; 13% of patients in each group had a history of diabetes. The authors found that normoglycemic patients who remained in the ICU for more than 5 days, had a lower mortality (with a notable reduction in deaths due to multiple-organ failure with a septic focus). A number of other advantages were also observed in the normoglycemic group such as: decreased bloodstream infections, reduced incidence of renal failure, and fewer blood transfusions. Normoglycemic patients were administered more insulin, and it is not clear whether improved outcome in this group related to better glycemic control, or some other beneficial effect of insulin. For example, insulin has been shown to promote anabolism and decrease catabolism in skeletal muscle in patients with burn [46]. Insulin also inhibits TNF production in rats and could have similar effects in humans that are advantageous during acute illness [47].

Management of Hyperglycemia During Stress

Goals of therapy

Hyperglycemic patients with acute illness should have treatment directed at maintaining blood glucose concentration less than 11.1 mmol/L [40]. Maintaining normoglycemia in postoperative patients appears to confer additional benefit, and it is possible that a similar approach will be adopted in other groups of patients [48]. Nevertheless, this therapy cannot be more widely advocated until confirmatory data in other groups of patients are available.

Correcting underlying causes of hyperglycemia

The initial step in the management of stress hyperglycemia involves identifying and treating the most common precipitating causes; this includes discontinuing drugs that worsen glucose tolerance, correcting hypokalemia, and treating infection. In addition, ongoing caloric requirements should be carefully assessed since overfeeding promotes hyperglycemia. Caloric requirements for critically-ill patients can be estimated as 20–25 total cal/kg/IBW/day [49]. However, estimates of energy expenditure may overpredict caloric needs in patients with morbid obesity; the use of indirect calorimetry may be valuable in these patients to obtain a more accurate prediction of energy requirements. Restricting calories (e.g., "*permissive underfeeding*") has been advocated as means to prevent hyperglycemia and reduce infectious complications [50]. This approach has been used in patients receiving TPN as a means to diminish hyperglycemia associated with trauma or other acute stress conditions [51]. McCowen et al. randomized critically ill patients receiving TPN to either hypocaloric support (1000 cal/d) or calories targeted at a daily goal of 25 cal/kg/IBW [52]. They found that caloric restriction did not lower the incidence of hyperglycemia or infections. Furthermore, nitrogen balance was inferior in the hypocaloric group relative to the fully-supported group. In contrast, hypocaloric feeding appears to be of benefit in morbidly obese patients with critical illness; administration of approximately 22 cal/kg/IBW in these patients seems to be effective in reducing TPN-associated hyperglycemia and is without significant adverse effects [53].

Use of insulin during critical illness

Many critically ill patients require insulin to control hyperglycemia; as many as 50–75% of patients suffering a major thermal injury need insulin at some point during their hospital course [1]. Insulin lowers blood glucose in part by diminishing hepatic glucose production; insulin-mediated enhancement of glucokinase gene transcription may play a significant role in this process [54]. Insulin also increases glucose uptake in insulin-sensitive

tissues through its effects on the GLUT4 transporter [55]. Insulin administration in hospitalized patients is commonly guided using a "sliding scale" format in which regular insulin is administered subcutaneously with the dose proportionate to the degree of hyperglycemia. Queale et al., in a study of hospitalized diabetics found that glycemic control was suboptimal in patients managed with sliding scale protocols (40% experienced hyperglycemic episodes) [56]. Recurrent hyperglycemia is inevitable with the sliding scale since most regimens do not provide basal coverage with long-acting insulin (e.g., NPH), and do not call for insulin if the blood glucose is normal. Therefore, if sliding scale coverage is prescribed, long-acting insulin should be administered concurrently [56].

Continuous infusion has been advocated as the preferred method of insulin administration in critically-ill patients [57]. There are several reasons why this approach makes sense in this population. First, problems with erratic absorption commonly seen with subcutaneous injection are eliminated since the insulin is infused directly into the circulation. Second, continuous infusion enables the insulin dose to be more rapidly and accurately titrated relative to the subcutaneous route. Third, ICU patients who are receiving a continuous caloric load with tube feeding or TPN lack a postprandial period. Their insulin requirements are therefore relatively stable throughout the day and it seems appropriate to maintain a constant influx of insulin with an infusion. A recent review of the management of diabetes during critical illness advocated continuous infusion as the preferred method of insulin administration in patients with type I and type II diabetes [57]. The use of insulin infusions may be simplified by using a dosing nonogram. A recent study of critically ill diabetic and non-diabetic patients compared blood glucose control using sliding scale insulin coverage with a continuous insulin infusion that was adjusted using a nomogram (Fig. 2) [58]. The authors found that the nonogram enabled more rapid control of blood glucose without any increase in frequency of hypoglycemia. Once the target blood glucose is attained, frequent monitoring of blood glucose (e.g., q 4 hrs) should be continued since the signs and symptoms of hypoglycemia may be masked in ICU patients. Intravenous dextrose should also be administered (unless significant hyperglycemia is present) to minimize the risk of hypoglycemia and provide a substrate for insulin. The insulin infusion should be stopped or markedly reduced in patients in whom tube feeding is interrupted in order to prevent hypoglycemia. In addition, an improvement in insulin sensitivity typically occurs in patients who are recovering from critical illness; hypoglycemia could ensue if this change is not anticipated.

TPN and hyperglycemia

As many as 25% of stressed patients receiving TPN will experience hyperglycemia [59]. A recent study found that TPN-induced hyperglycemia was most strongly associated with administration of dextrose in excess of 5 mg/kg/min [60]. Patients receiving enteral nutrition appear to be less prone to develop hyperglycemia than those fed parenterally; this is due in part to a lesser caloric intake secondary to frequent interruption of tube feeding (e.g., due to ileus, during procedures or transport). In addition, hyperglycemia is also moderated during enteral feeding by stimulation of hepatic glucose uptake secondary to first-pass splanchnic glucose uptake; this effect is not seen when nutrients are administered parenterally [61]. Moore et al. performed a meta-analysis of trials comparing TPN with enteral nutrition and concluded that TPN is associated with a higher rate of infection [62]. However, retrospective analysis of the data indicated that patients receiving TPN had a higher caloric load than those fed enterally; this in turn promoted hyperglycemia that could account for the increased rate of infection [52]. TPN-associated hyperglycemia and its complications may therefore be minimized by careful assessment of caloric requirements.

Several authors have provided guidelines to optimize glycemic control in patients receiving TPN [63,64]. As mentioned above, careful assessment of caloric requirements reduces the likelihood of overfeeding. In addition, permissive underfeeding of calories appears to be a safe and effective way to prevent TPN-induced hyperglycemia in obese patients [53]. The initial dextrose dose in TPN can be estimated as 150–200 gm in patients at low risk for hyperglycemia, and 100 gm for patients with preexisting hyperglycemia or with conditions placing them at high-risk (e.g., preexisting diabetes, glucocorticoid therapy, obesity, sepsis) [63]. If insulin is required to control hyperglycemia during TPN in critically-ill patients, it is probably best administered as a continuous infusion; this allows insulin to be adjusted independently of the TPN solution. An alternate approach involves adding regular insulin to the TPN and adjusting the dose on a daily basis [63,64]; the downside of this method is that the TPN and insulin cannot be manipulated independently, and hypoglycemia may necessitate stopping the TPN. Substitution of dextrose calories with lipid may also be useful in facilitating glucose control; up to 30% of dextrose calories in the TPN can be replaced by fat in order to decrease the carbohydrate load. It should be remembered however that all parenteral lipid emulsions currently available in the US are high in omega-6 polyunsaturated fatty acids (e.g., linoleic acid, arachidonic acid) that are inflammatory and immunosuppressive [65].

INSULIN INFUSION PROTOCOL - Regular Human Insulin Only (ICU only)

GOAL: The goal is to maintain serum glucose between 7 and 11.5 mmol/L

MONITORING: Check glucose **q1h** (either capillary or blood) until stable **(3 values in desired range).** Checks can be reduced to q2h x 4 hours → q4h if blood glucose remains in desired range. Restart q1h checking if any change in insulin infusion rate occurs. If glucose is changing rapidly (even if in the desired range) **OR** if in a critical range (<3.5 or >20mmol/L) q30minute checks may be needed. However, blood glucose will not change significantly in <30 minutes with any change in insulin.

Initiating Insulin Infusion

Glucose	11.5-14mmol/L	14.1-17mmol/L	17.1-20mmol/L	20.1-24mmol/L	>24mmol/L
	Give 3 units insulin IVP and start @ 2 units/hr	Give 6 units insulin IVP and start @ 2 units/hr	Give 8 units insulin IVP and start @ 2 units/hr	Give 10 units insulin IVP and start @ 2 units/hr	Call MD for orders

Ongoing Insulin Infusion:

Below Desired Range (7-11.5mmol/L)

Glucose Level	Infusion Rate of 1-3 units/hr	Infusion Rate of 4-6 units/hr	Infusion Rate of 7-9 units/hr	Infusion Rate of 10-12 units/hr	Infusion Rate of 13-16 units/hr	Infusion Rate of > 16 units/hr
< 3.5mmol/L	D/C Infusion and give 1 amp D50 IVP					
3.5-4.5mmol/L	D/C Infusion: Re-check glucose in 1 hour. If >7, re-start but decrease rate by 1unit/hr.		D/C Infusion: Re-check glucose in 1 hour. If >7, re-start but decrease rate by 2 unit/hr.		D/C Infusion: Re-check glucose in 1 hour, If >7, re-start but decrease rate by 3 unit/hr.	
4.6-5.5mmol/L	D/C Infusion: Re-check glucose in 1 hour, if > 7, re-start but decrease rate by 1 unit/hr.	Decrease Infusion by 50%				
5.6-7mmol/L	Decrease Infusion by 1 unit/hr	Decrease Infusion by 2 units/hr	Decrease Infusion by 3 units/hr	Decrease Infusion by 4 units/ hr	Decrease Infusion by 5 units/hr	Decrease Infusion by 6 units/hr

In Desired Range (7-11.5mmol/L)

7-11.5mmol/L	NO CHANGES NOW If glucose continues to decrease within the desired range over 3 consecutive hours, decrease rate by 1 unit/hr.	NO CHANGES NOW If glucose continues to decrease within the desired range over 3 consecutive hours, decrease rate by 2 unit/hr..

Above Desired Range (7-11.5mmol/L)

Glucose Level	Infusion Rate of 1-5 units/hr	Infusion Rate of 6-10 units/hr	Infusion Rate of 11-16 units/hr	Infusion Rate of > 16 units/hr
11.5-14mmol/L	Give 2 units insulin IVP and increase Infusion by 1 unit/hr	Give 3 units insulin IVP and increase Infusion by 2 units/hr	Give 3 units insulin IVP and increase Infusion by 3 units/hr	Call Physician for New Order
14.1-17mmol/L	Give 3 units insulin IVP and increase Infusion by 1 unit/hr	Give 5 units insulin IVP and increase Infusion by 2 units/hr	Give 5 units insulin IVP and increase Infusion by 3 units/hr	
17.1-20mmol/L	Give 8 units insulin IVP and increase Infusion by 1 unit/hr	Give 8 units insulin IVP and increase Infusion by 2 units/hr	Give 8 units insulin IVP and increase Infusion by 3 units/hr	
20.1-24mmol/L	Give 10 units insulin IVP and increase Infusion by 1 unit/hr	Give 10 units insulin IVP and increase Infusion by 2 units/hr	Give 10 units insulin IVP and increase Infusion by 3 units/hr	
> 24mmol/L	Call Physician for New Order			

Fig. 2. Continuous insulin dosing nomogram for "conventional" insulin therapy. From: Brown G, Dodek P. Intravenous insulin nomogram improves blood glucose control in the critically ill. Crit Care Medicine 2001;29:1714–1719. Used by permission. (See Van den Berghe et al. [45] for "intensive" approach to insulin therapy).

Adverse effects of insulin therapy

The major adverse effect of insulin therapy is hypoglycemia. As mentioned above, concurrent administration of dextrose and frequent monitoring of blood glucose is particularly important in ICU patients since signs and symptoms of hypoglycemia are often masked. Control of blood glucose in stressed patients with insulin resistance may be difficult and require administration of large doses of insulin. This in turn may promote salt and water retention that could pose problems for patients with heart or kidney failure [66]. Some clinicians are reluctant to use high doses of insulin because of concerns with increasing hepatic glucose uptake and promoting development of fatty liver. However in contrast to skeletal muscle and fat, hepatic glucose uptake is not mediated by insulin and instead is dependent on the concentration of glucose in the portal vein [67]. Therefore, administration of insulin *per se* should not cause hepatic steatosis assuming that

adequate glycemic control is maintained. The pathogenesis of hepatic steatosis during critical illness may relate more to the effects of cytokines or an acquired abnormality of triglyceride secretion [23,67,68].

Summary

Stress hyperglycemia refers to transient elevations in blood glucose concentration in acutely ill patients not previously known to have diabetes. The pathogenesis of stress hyperglycemia relates to abnormalities in glucose production and utilization consequent to activation of the HPA and release of counterregulatory hormones and cytokines. Hyperglycemia in both diabetic and non-diabetic patients is associated with increased morbidity and mortality. Management of stress hyperglycemia includes identifying and correcting underlying causes. The use of insulin is frequently necessary to attain glycemic control. Continuous infusion appears to be the preferred route of insulin administration in many critically ill patients. The use of "sliding scale" protocols in the absence of basal insulin coverage is associated with poor glycemic control and is not recommended. Aggressive treatment of hyperglycemia is associated with reduced complications and decreased mortality in certain patient groups; recent data in postoperative ICU patients demonstrated reduced morbidity and mortality associated with maintaining normoglycemia. Confirmatory studies in other patient populations are necessary before this approach can be more widely advocated.

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