HYPERGLYCEMIA IN THE CRITICALLY ILL: CONSEQUENCES AND TREATMENT

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ABSTRACT
Hyperglycemia has long been recognized as a common occurrence in the critically ill, even without a history of diabetes. During times of stress or injury, normal glucose metabolism is altered because of changes in endocrine secretions and peripheral insulin resistance, resulting in stress hyperglycemia. Although hyperglycemia is a normal part of the stress response, it has recently been recognized to be associated with increased mortality and morbidity. Furthermore, insulin therapy has been shown to decrease mortality and improve other patient outcomes. However, many questions remain unanswered concerning the efficacy of insulin therapy. It is still unclear how tight glucose control should be and which patient types benefit from the treatment. More research is needed before insulin therapy can be widely used.
Hyperglycemia in the Critically Ill: Consequences and Treatment

Introduction

Hyperglycemia has long been recognized as a common occurrence in critically ill patients, even without a history of diabetes. Although there are few studies investigating the prevalence of stress hyperglycemia, one review reported that 38% of patients admitted to a general hospital had hyperglycemic episodes, 16% of which had no previous history of diabetes mellitus (Cortjsens et al., 2006). Stress hyperglycemia is thought to be the body’s adaptive response to stress or injury (Gearhart & Parbhoo, 2006; Falciglia, 2007). In the past, this response to injury was believed to be beneficial during critical illness (Langouche & Van den Berghe, 2006). However, recently researchers have found evidence that hyperglycemia in critically ill patients can pose a greater risk of mortality and morbidity. Furthermore, the evidence suggests that insulin therapy to control stress hyperglycemia can reduce mortality and improve overall patient outcome. Some studies show that insulin therapy results in reduced hospital and ICU length of stay, decreased need for antibiotics, fewer blood transfusions, reduced organ failure, and other benefits in critically ill patients (Van den Berghe et al., 2001; Van den Berghe et al., 2006; Krinsley, 2003; Bochicchio, Salzano, Joshi, Bochicchio, & Scalea, 2002). The landmark study on hyperglycemia in surgical ICU patients by Van den Berghe and colleagues in 2001 brought new light to the seriousness of hyperglycemia and has elicited the need for further research (Van den Berghe et al., 2001).

This review will examine the mechanisms of stress hyperglycemia and the changes in normal glucose metabolism during critical illness. The purpose of this literature review is to investigate the consequences of stress hyperglycemia and consider if insulin therapy would be an effective solution and treatment.
Keywords: hyperglycemia, ICU, critically ill, insulin, hospitalization, stress.

**Stress and Metabolism**

Glucose homeostasis is vital to the body’s overall homeostasis. Glucose is the primary energy source for most cells in the body. Erythrocytes and neurons depend solely on glucose for energy (Saladin, 2007). Blood glucose levels must be maintained within a narrow range to avoid tissue damage and other problems. During times of stress this balance can be disrupted. In order to understand the impact of stress and the mechanisms of stress hyperglycemia, normal glucose metabolism must be discussed.

**Normal Glucose Metabolism**

Glucose is absorbed in the small intestine via a sodium-dependent active transporter: sodium-glucose transporter 1 or SGLT1. Following absorption into enterocytes, glucose enters the portal circulation and is transported to the liver. The liver is the main site for glucose metabolism. Glycolysis, glycogenesis, glycogenolysis, and gluconeogenesis all take place in the liver. Glycolysis is the breakdown of a glucose molecule into pyruvate. Pyruvate is oxidized and enters the Citric Acid Cycle, producing substrates that enter the electron transport chain to finally produce ATP, or energy. Glycogenesis is the synthesis of glycogen, the long-term storage form of glucose. Glycogenolysis is the breakdown of glycogen to give glucose. Gluconeogenesis is the production of glucose from non-carbohydrate precursor molecules (Gropper, Smith, & Groff, 2005).

Glycolysis, glycogenesis, glycogenolysis, and gluconeogenesis are under the control of insulin and glucagon. Insulin is secreted after meals or when blood glucose levels rise and promotes glycolysis and glycogenesis. Glucagon is secreted in between meals or when blood glucose levels get too low, and promotes glycogenolysis and gluconeogenesis. Through the
action of insulin and glucagon, blood glucose levels are maintained within the normal and healthy range (Gropper et al., 2005). Normal fasting blood glucose levels are 70 to 100 mg/dL. Fasting blood glucose levels between 100 and 125 mg/dL are considered pre-diabetic and 126 mg/dL and higher is considered diabetic (Whitney & Rolfes, 2008).

After a meal, glucose enters glycolysis or glycogenesis in the liver and the remaining glucose continues into the systemic blood supply and is taken up by the kidneys, adipose tissue, muscle, and other tissues (Gropper et al., 2005). Glucose utilizes a carrier-mediated transport system for entry into cells. There are several different isoforms of the carriers called glucose transporters, which are abbreviated GLUT. Some of these isoforms are insulin sensitive and others are not (Gropper et al., 2005). For the purposes of this paper, the most important GLUT isoform is GLUT4. GLUT4 is present mostly in adipocytes and cardiac and skeletal muscle. GLUT4 is regulated by insulin. Under normal circumstances, when blood glucose becomes too high after a meal, pancreatic β cells secrete insulin and cause GLUT4 to translocate to the cell membrane. This results in an increased uptake of glucose into fat cells and skeletal and cardiac muscle cells and thereby decreases blood glucose levels (Gropper et al., 2005).

**Physiological Effects of Stress**

*Definitions and Types of Stress.* There are many types of stress associated with hospitalization and illness. There are psychological, emotional, and physical stressors. It is important to distinguish which type of stress contributes to the hypermetabolic state associated with critical illness and to define stress.

Mechanick (2006) reported in a review of the mechanisms of stress hyperglycemia that, “A ‘stressor’ is an event that constitutes a threat to homeostasis. ‘Stress,’ on the other hand, is the response to a stressor and consists of a physiologic component…and a behavioral
component” (Mechanick, 2006, p. 157). Stressors can be further categorized as either cognitive or non-cognitive stressors. Cognitive stressors are usually emotions such as fear, depression, or bereavement (Mechanick, 2006). Non-cognitive stressors can be physical such as injury, surgery, infection, or pain (Saladin, 2007). The stress response is the body’s uniform reaction to all types of stressors (Saladin, 2007). Stress hyperglycemia is one of the physiological components of the stress response caused by cognitive and non-cognitive stressors associated with hospitalization and illness.

**Endocrine Effects of Stress.** As part of the physiological component of the stress response, the body’s hormone secretions change. An increase in counter-regulatory hormones is the major change that occurs during stress. Counter-regulatory hormones are hormones that oppose the action of insulin (McCowan, Malhotra, & Bistrian, 2001). During critical illness, the hypothalamic-pituitary-adrenal (HPA) axis is activated (Marik & Raghavan, 2004). This launches a cascade of endocrine secretions. The hypothalamus releases corticotropin-releasing hormone, which stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal glands to cause secretion of cortisol and other glucocorticoids, which are considered counter-regulatory hormones (Saladin, 2007). The secretion of other counter-regulatory hormones also increases due to activation of the HPA axis such as norepinephrine, epinephrine, glucagon, and growth hormone (Marik & Raghavan, 2004). It is believed that while secretion of these counter-regulatory hormones is increased, insulin secretion is actually decreased (Marik & Raghavan, 2004).

**Metabolic Effects of Stress.** The increase in counter-regulatory hormones during stress has many metabolic repercussions. Norepinephrine, epinephrine, growth hormone, cortisol, and glucagon induce glycogenolysis and gluconeogenesis, causing increased hepatic glucose
production and decreased peripheral glucose uptake (Mechanick, 2006). This shift in metabolic activity is driven by fat and protein catabolism, which provide the necessary precursors for gluconeogenesis. Cortisol promotes proteolysis to provide amino acids such as alanine for gluconeogenesis. Epinephrine and norepinephrine induce the breakdown of fats, providing glycerol for gluconeogenesis (Gearhart & Parbhoo, 2006). Hepatic and skeletal muscle glycogenolysis is also increased by the presence of norepinephrine and epinephrine (Gearhart & Parbhoo, 2006). All of these processes ensure that the brain and other vital organs receive an adequate amount of glucose (Gearhart & Parbhoo, 2006).

Stress and critical illness have numerous effects on physiology. The stress response changes endocrine secretions and causes many metabolic changes. The deviation from normal resting glucose metabolism combined with decreased insulin secretion and peripheral insulin resistance during critical illness ultimately leads to stress hyperglycemia.

**Stress Hyperglycemia**

**Prevalence**

Researchers agree that stress hyperglycemia is very common among critically ill patients (Langouche & Van den Berghe, 2006). However, it is difficult to estimate exactly how widespread stress hyperglycemia is among hospitalized patients because few studies are available on prevalence and they usually have a small sample size (Corstjens et al., 2006). A more strict definition of hyperglycemia is needed in order to determine the prevalence of stress hyperglycemia. Hyperglycemia is generally defined as plasma glucose greater than 200 mg/dL (McCowen et al., 2001). However, some researchers define hyperglycemia differently for their studies.
DiNardo and colleagues (2004) claimed in their review that one third of patients in tertiary care facilities were hyperglycemic (DiNardo, Korytkowski, & Siminerio, 2004). Another review reported a study that showed 38% of patients admitted to a general hospital had elevated blood glucose levels while hospitalized (Corstjens et al., 2006).

The frequency of stress hyperglycemia also depends on the type of patients being studied. In a study of medical ICU patients, 23% of patients had blood glucose levels above 11.1 mmol/L upon admission (Corstjens et al., 2006). In contrast, a different study found that 86% of thoracoscopic ICU patients had blood glucose above 6.1 mmol/L upon admission and 96% of those patients became hyperglycemic during their time in the ICU (Corstjens et al., 2006). Hyperglycemia is also more common among older patients and patients receiving total parenteral nutrition at rates greater than 4 mg/kg/min (McCowan et al., 2001).

**Mechanisms and Causes**

The exact cause and mechanisms of stress hyperglycemia are complicated and not completely understood. Normal homeostatic mechanisms would be expected to prevent harmful hyperglycemia. However, as mentioned earlier, hyperglycemia can be a result of the stress response. There is a good body of evidence to suggest that a strong contributor to stress hyperglycemia is the increased hepatic gluconeogenesis caused by higher concentrations of the stress hormones.

In a study of the effects of stress hormones, for three days healthy volunteers were given epinephrine, glucagon, and cortisol in doses characteristic of severe stress. The results showed a 60% to 80% increase in blood glucose levels regardless of increased plasma insulin concentrations (McCowan et al., 2001). In one animal study, a 70-hour infusion of cortisol, glucagon, and catecholamines given to dogs resulted in a significant increase in net hepatic
glucose production. There was no change in peripheral glucose absorption even with increased insulin concentrations (McCowan et al., 2001). Furthermore, a human study tracking stable isotopes in trauma patients also showed that hyperglycemia was attributed mostly to increased hepatic glucose production. In this study, overall glucose clearance and oxidation were similar to healthy controls, but hepatic glucose production was significantly higher in the trauma patients (McCowan et al., 2001).

Other mechanisms or causes of stress hyperglycemia have also been put forward. Cellular glycogenesis seems to be compromised in critical illness (McCowan et al., 2001). Decreased insulin concentrations are common among critically ill patients with stress hyperglycemia (DiNardo et al., 2004). It has been suggested that stress hyperglycemia is only manifested in individuals who have an inherent metabolic defect and cannot compensate adequate amounts of insulin for the increased glucose production caused by stress (Falciglia, 2007). Insulin resistance is also a contributor to stress hyperglycemia in critically ill patients (Mechanick, 2006).

**Insulin Resistance**

During critical illness, parts of the insulin-signaling pathway that cause GLUT4 to translocate to the plasma membrane are impaired (McCowan et al., 2001). This is a result of the action of stress hormones such as epinephrine, growth hormone, and cortisol. Each of these hormones contributes to insulin resistance in a different way.

Epinephrine has several effects on glucose metabolism. Epinephrine increases glycogenolysis in skeletal muscles (McCowan et al., 2001). One of the intermediate molecules produced in glycogenolysis inhibits glycolysis. This also inhibits glucose uptake because glucose uptake is closely coupled with glycolysis (McCowan et al., 2001). In a human
experiment where subjects were given several stress hormones to imitate critical illness, when epinephrine infusion was stopped while maintaining infusion of the other hormones, plasma insulin increased, insulin sensitivity improved, and free fatty acid levels decreased (McCown et al., 2001). This suggests that epinephrine promotes insulin resistance and inhibits insulin secretion.

Glucocorticoids such as cortisol also encourage insulin resistance. It is most likely that this is accomplished by inhibiting translocation of GLUT4 to the plasma membrane by down regulating proteins in the insulin-signaling cascade (McCown et al., 2001). Growth hormone, one of the counter-regulatory hormones, seems to have the same effect as glucocorticoids (McCown et al., 2001). Growth hormone also decreases the number of insulin receptors and inhibits the activation of the insulin-signaling pathway (Marik & Raghavan, 2004).

Other factors also contribute to insulin resistance in critical illness. Bed rest and the immobilization of critically ill patients are factors in the development of insulin resistance (Langouche & Van den Berghe, 2006). Critically ill patients have no exercise-stimulated uptake of glucose in skeletal muscles (Langouche & Van den Berghe, 2006). Even in healthy volunteers, six days of bed rest caused lower glucose tolerance and decreased insulin response (McCown et al., 2001). There is also some evidence that free fatty acids have an inhibitory effect on the insulin-signaling pathway (McCown et al., 2001). This is significant because lipolysis is increased by the stress response and this could explain at least part of what causes hyperglycemia in the critically ill.

**Stress Hyperglycemia and Mortality**

Since the first landmark study by Van den Berghe and colleagues in 2001, much research has been conducted to examine the effects of stress hyperglycemia among critically ill patients.
Many of these studies have found that hyperglycemia in the critically ill has detrimental effects on patient outcome. These effects are most evident when compared to patients receiving insulin therapy. Researchers have found that hyperglycemia does not only affect morbidity; it also can have a significant effect on mortality.

In 2001, Van den Berghe and colleagues conducted a groundbreaking study on hyperglycemia in surgical ICU patients. The study included 1,548 patients admitted to the surgical ICU and who required mechanical ventilation. At the time of admission, patients were randomly assigned to a conventional or intensive insulin therapy group. Conventional therapy consisted of a continuous insulin infusion only when blood glucose exceeded 215 mg/dL with a target range of 180-200 mg/dL. Intensive insulin therapy consisted of a continuous insulin infusion if blood glucose exceeded 110 mg/dL with a target range of 80-110 mg/dL. All patients received standardized total parenteral, combined parenteral and enteral, or total enteral feeding. The conventional treatment group had a mortality rate of 8.0% whereas the intensive treatment group only had a 4.6% mortality rate, showing a 42% risk reduction when intensive insulin therapy was used. This difference can be seen in Figure 1. The reduction in mortality was greatest in patients with ICU stays of 5 days or longer. In the long-stay patients, 10.6% mortality was observed in the intensive treatment group compared with 20.2% in the conventional treatment group (Van den Berghe et al., 2001).

This study was the first evidence that stress hyperglycemia might lead to increased morbidity and mortality in the critically ill. The results suggest that insulin therapy can help to reduce the risk of death in critically ill patients when slightly elevated blood glucose levels or hyperglycemia are present. The weaknesses of this study were the high nurse to patient ratio, which may not be feasible in most institutions, and it was a single-center trial. The results of this
study have generated further research investigating the link between mortality and hyperglycemia in critically ill patients.

Figure 1. Kaplan-Moier curves showing cumulative survival of patients who received intensive insulin treatment or conventional treatment in the intensive care unit (ICU). Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the difference between the treatment groups was significant (From Van den Berghe et al., 2001).

Krinsley (2003) conducted a retrospective study examining the correlation between mean plasma glucose level and hospital mortality in ICU patients. In this study, plasma glucose levels were monitored throughout the ICU stay of a heterogeneous population of 1,826 patients. The mean glucose value was then calculated for each patient and each patient was put into the category of “survivor” or “non-survivor”. Initial and maximum glucose values were also analyzed. The results showed an increasing hospital mortality rate with increasing blood glucose levels, summarized in Table 1. Higher maximum blood glucose levels also increased mortality. The correlation was not as strong for initial glucose values. Although diabetes was present in 22.4% of the patients studied, there was no difference in mortality between diabetic and non-diabetic patients. The greatest difference in mean glucose values was between the non-diabetic
survivor group (123.8 mg/dL) and the non-diabetic non-survivor group (162.8 mg/dL). The mean glucose value of all survivors was 137.9 mg/dL and the mean glucose value of all non-survivors was 172.0 mg/dL (P<0.001) (Krinsley, 2003).

Table 1. Hospital Mortality Rate and Mean Glucose Value

<table>
<thead>
<tr>
<th>Mean (mg/dL)</th>
<th>Mortality rate (%)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-99</td>
<td>9.6</td>
<td>264</td>
</tr>
<tr>
<td>100-119</td>
<td>12.2</td>
<td>491</td>
</tr>
<tr>
<td>120-139</td>
<td>15.1</td>
<td>338</td>
</tr>
<tr>
<td>140-159</td>
<td>18.8</td>
<td>202</td>
</tr>
<tr>
<td>160-179</td>
<td>28.4</td>
<td>141</td>
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<tr>
<td>180-199</td>
<td>29.4</td>
<td>102</td>
</tr>
<tr>
<td>200-249</td>
<td>37.5</td>
<td>144</td>
</tr>
<tr>
<td>250-299</td>
<td>32.9</td>
<td>70</td>
</tr>
<tr>
<td>&gt;300</td>
<td>42.5</td>
<td>40</td>
</tr>
</tbody>
</table>

From Krinsley, 2003.

This study is significant because of its large sample size and because it suggests that even a slightly elevated blood glucose level is associated with increased mortality. However, a causal relationship cannot be determined from the results. It is difficult to tell from this study whether the increased mortality is a result of hyperglycemia or if hyperglycemia is a marker of increased risk of mortality. Furthermore, each patient had a different length of stay in the ICU and therefore the number of glucose values used to calculate the mean blood glucose was different for each patient.
A similar study investigated the effect of newly recognized hyperglycemia on hospital mortality and 45-day mortality among diabetic and non-diabetic elderly patients in a sub-intensive care unit. Hyperglycemia was defined as >180 mg/dL. This study included 1,229 patients, 333 or 27.1% of which had a diagnosis of diabetes mellitus. Patients were categorized based on fasting serum glucose concentrations within 24 hours of admission in the following way: Group A (60-126 mg/dL), Group B (127-180 mg/dL), Group C (≥ 181 mg/dL). Hyperglycemic episodes in non-diabetic patients were treated with insulin without a target range. The researchers found that in non-diabetic patients with newly recognized hyperglycemia, the in-hospital mortality rates increased from Group A (11.2%) to Group B (17.3%) to Group C (34.4%). For patients with diabetes mellitus, in-hospital mortality for all groups combined was lower and in-hospital mortality within groups was lower (8.8%, 13.6%, 12.6% for A, B, and C respectively). The 45-day mortality for non-diabetic patients with newly recognized hyperglycemia was even higher than the in-hospital mortality: Group A 17.5%, Group B 25.7%, Group C 42% (Sleiman et al., 2008).

The data from the Krinsley (2003) study and the Sleiman (2008) study concerning diabetic patients suggest that hyperglycemia in non-diabetic critically ill patients is more damaging than hyperglycemia in diabetic critically ill patients. In both studies high blood glucose values in non-diabetic patients were associated with higher mortality compared to mortality of diabetic patients. It is possible this is due to more strict control of glycemic values in diabetic patients with exogenous insulin. If that is true, this could be used as rationale for the use of insulin therapy in critically ill. However, the risks associated with insulin therapy must be taken into account before it can be used safely.
A smaller study examined the effect of poor glycemic control on all patients admitted to a surgical ICU for 48 hours or longer during a six-month period. The sample size was 103. The average age of the subjects studied was 50 and 80.30% were male. An insulin protocol was in place that consisted of administration of subcutaneous insulin if blood glucose exceeded 140 mg/dL. All blood glucose values that were obtained during the ICU stay were averaged for each patient and were categorized as “controlled” if the average was $<140$ mg/dL or “non-controlled” if the average was $\geq 141$ mg/dL. As shown in Figure 1, mortality was 9.09% for controlled patients and 22.22% for non-controlled patients. Figure 2 shows the mortality rates corresponding to different levels of glycemic control. Subjects in the non-controlled group were significantly older than the controlled group, but Injury Severity Scores (ISS) were similar (Gale, Sicoutris, Reilly, Schwab, & Gracias, 2007). Injury Severity Scores are assigned based on the Abbreviated Injury Scale (a scale of one through six, one being minor and six being unsurvivable) scores of injuries in six body regions: head, face, chest, abdomen, extremities, and external. The scores of the three most severely injured regions are squared and added together, giving the ISS (Trauma.org, 2009).

Figure 1. Mortality versus level of glycemic control—all 103 patients (From Gale et al., 2007).
Figure 2. Percent mortality by level of glycemic control—all patients (From Gale et al., 2007).

The weakness of this study is its small sample size. Regardless, the results are consistent with those of all the studies discussed thus far. In order to better interpret the results, it would be helpful to know how many patients in the “controlled” group received insulin compared to the “non-controlled” group. This would help determine if insulin helped to reduce mortality.

Another prospective study conducted by Bo chicchio and colleagues (2005) investigated the association between admission glucose values and mortality and morbidity in trauma patients who underwent surgery after admission. The sample size was 252 patients. Subjects with a diagnosis of diabetes mellitus were excluded from the study. Upon admission to the trauma center, patients’ serum glucose values were obtained and were categorized as <200 mg/dL or ≥ 200 mg/dL. ISS were also assigned. The results showed that the group with glucose ≥ 200 mg/dL had a significantly greater mortality even when adjusted for ISS and age (Bo chicchio et al., 2005).

There were a couple weaknesses to this study. Since this study only included trauma patients, the results are not generalizable to all patient populations. Furthermore, the researchers only looked at admission glucose values, which were found to be less predictive of mortality in the Krinsley (2003) study. A larger sample size would also be needed for the results to be more statistically significant. Despite the weaknesses, one important conclusion can be drawn from
the results. A higher mortality even when adjusted for ISS and age imply that hyperglycemia is not just a marker of a higher risk of death, but may be itself a risk factor for increased mortality.

**Insulin Therapy**

The evidence suggests that there is a strong correlation between hyperglycemia and increased mortality in the critically ill. Since this was recognized, researchers have investigated the effectiveness of insulin therapy in reducing mortality as well as morbidity. Several of the studies already described have also shown a reduction in hospital and ICU length of stay, infection, inflammation and sepsis, organ failure, and other patient outcome measures. Although insulin therapy may have many benefits, it is a very new treatment option and also has some risks.

**Benefits**

*Mortality.* Krinsley (2004) conducted a study examining the effect of a glucose management protocol on mortality in adult ICU patients. The goal of the protocol was to maintain blood glucose below 140 mg/dL. Nurses obtained glycemic values every three hours initially and then less frequently if values were stable. If blood glucose exceeded 200 mg/dL on two consecutive occasions, continuous intravenous insulin was given. Researchers compared outcomes of 800 patients admitted to the ICU immediately before the protocol was put into practice to outcomes of 800 patients admitted directly after the protocol was started. The baseline group had a mortality of 20.9% compared to 14.8% in the treatment group, representing a 29.3% decrease in mortality when the glucose management protocol was in place (K rinsley, 2004).

The weakness of this study, within the study design, was that it did not compare patient groups that were simultaneously getting different treatments. However, the researchers claim
that quality and quantity of care did not change before and after the protocol was put in place. The strength of this study is that it compared outcomes of patients that received no insulin therapy to patients who received insulin instead of comparing patient outcomes of two different insulin therapy treatments, such as in the Van den Berghe (2001) study.

Van den Berghe and colleagues (2006) conducted a follow-up experiment to investigate the effect of intensive insulin therapy versus conventional insulin therapy in medical ICU patients. The study included 1,200 patients that were expected to stay 3 days or longer in the ICU and who were not able to receive oral nutrition. This criterion was chosen because of the evidence in the 2001 Van den Berghe study that intensive insulin therapy was most beneficial in patients requiring a longer stay in the ICU. The same treatment groups and insulin protocols were used as in their 2001 study. The authors found a reduction in mortality only after the third day in the ICU, from 52.5 % to 43.0 % in the intensive treatment group. After the fifth day, intensive insulin therapy reduced mortality from 54.9 % to 45.9 % (Van den Berghe et al., 2006).

This study suggests that hyperglycemia in the critically ill may have the strongest effect on mortality among critically ill patients that are hospitalized for longer time periods, which is consistent with the findings of the 2001 study (Van den Berghe et al., 2001). The authors suggested that insulin is most beneficial after a longer time period possibly because the benefits of insulin therapy take time to be manifested (Van den Berghe et al., 2006). However, this explanation conflicts with the results of the 2001 study and the Krinsley (2004) study, which showed a benefit from insulin therapy even in patients with ICU stays less than three days (Van den Berghe et al., 2001).
Hospital and ICU length of stay. A decreased hospital and ICU length of stay is one of the benefits of insulin therapy that has been observed in critically ill patients receiving this new type of treatment. Van den Berghe (2001) was the first to recognize this correlation. The researchers noted a reduced ICU length of stay but not overall hospital length of stay with intensive insulin therapy. The decreased ICU length of stay was most apparent in patients receiving five days or more of intensive care (Van den Berghe et al., 2001). In contrast, Van den Berghe and colleagues (2006) found that “intensive insulin therapy for at least a third day, as compared with conventional therapy, accelerated weaning from mechanical ventilation, discharge from the ICU, and discharge from the hospital” (Van den Berghe et al., 2006, p. 455).

Bochicchio and colleagues (2005) found that hyperglycemic trauma patients also had significantly longer ICU and hospital lengths of stay, as shown in Figure 3, even when adjusted for age and ISS (Bochicchio et al., 2005). Similarly, Krinsley (2004) found that after a glucose management protocol was put in place, mean ICU length of stay decreased from 3.58 days to 3.19 days (Krintsley, 2004).

![Figure 3](image)

Figure 3. Mean ICU and hospital length of stay (days) stratified by serum glucose level (mg/dL) (*P < 0.05) (From Bochicchio et al., 2005).
Infection and need for antibiotics. Some studies show that insulin therapy reduces the incidence of infection, thereby reducing the need for antibiotics. Bochicchio and colleagues (2005) found that hyperglycemic patients had a 48% infection rate compared to 29% in normoglycemic patients (Bochicchio et al., 2005). In Van den Berghe (2001) the intensive treatment group had a lower incidence of bacteremia and therefore a decreased need for antibiotics (Van den Berghe et al., 2001). A prospective non-randomized trial compared outcomes of 271 ICU patients receiving conventional or intensive insulin therapy as outlined by Van den Berghe and colleagues (2001). The researchers found a reduction in secondary infections from 21.5% in the conventional group to 16.0% in the intensive group (Toft, Jorgensen, Toennesen, & Christiansen, 2006). Furthermore, a trial with the same study design as Van den Berghe (2001) observed a decrease in the length of antibiotic use from a median of 12 days (conventional treatment) to 9 days (intensive treatment) (Hansen, Thiel, Wouters, Christiansen, & Van den Berghe, 2003).

Although there is good evidence for a decreased occurrence of infection in patients receiving insulin therapy, some studies have found no difference. The 2006 Van den Berghe study found no significant reduction in the occurrence of bacteremia between the intensive and conventional treatment groups (Van den Berghe et al., 2006). Krinsley (2004) also found no difference in the incidence of infection in insulin treated patients compared to patients who did not receive insulin (Kminsley, 2004). The studies that found a reduction in infection mostly included surgical ICU patients. Van den Berghe (2006) included only medical ICU patients and Krinsley (2004) included a mixed population of ICU patients. This could account for their findings that insulin had no effect on infection.
Blood Transfusions. Another possible benefit of insulin therapy is a reduction in the number of blood transfusions. However, this finding has not been consistent. Toft and colleagues (2006) observed no difference in the number of blood transfusions between intensive and conventional treatment groups (Toft et al., 2006). Van den Berghe and colleagues (2001) found no difference in the number of patients who received blood transfusions between the intensive and conventional treatment groups. However, the median number of transfusions in the intensive insulin group was half of the median of the conventional insulin group (Van den Berghe et al., 2001). Furthermore, Krinsley (2004) noted a decrease in the percentage of patients receiving blood transfusions after the implementation of a glycemic management protocol, from 25.2% to 20.5% (P < 0.04). The mean number of units of packed RBCs received also decreased, from 3.79 units to 3.30 units (Krinsley, 2004).

Organ Failure. Renal dysfunction can be a complication of hyperglycemia in critically ill patients. Insulin therapy has been shown to reduce the need for hemofiltration or dialysis among critically ill. Krinsley (2004) observed a decrease in the number of patients with new renal dysfunction after the institution of a glycemic management protocol from 12 patients to 3 patients (Krinsley, 2004). Van den Berghe (2006) found that in patients with stays longer than three days in the ICU, acquired kidney injury decreased from 12.6% in the conventional treatment group to 8.3% in the intensive treatment group (Van den Berghe et al., 2006). Similarly, Toft and colleagues (2006) found that the number of patients who developed renal failure, and as a result required hemofiltration, decreased from 14.1% to 9.6% when intensive insulin therapy was used (Toft et al., 2006).

Other outcome measures. Other patient outcome measures that seem to be benefited from insulin therapy include a reduction in critical illness polyneuropathy, decreased incidence
of inflammation and sepsis, decreased hyperbilirubinemia, and more rapid weaning from mechanical ventilation (Van den Berghe et al., 2001; Van den Berghe et al., 2006; Krinsley, 2004; Toft et al., 2006). Figure 4 summarizes the relative risk reduction for patient outcome measures with the use of intensive insulin therapy based on the findings from Van den Berghe and colleagues (2001).

![Relative risk reduction (%)](image)

Figure 4. Relative risk reductions for key measures of ICU morbidity. *P <0.01; †P < 0.0001. Errors bars: 95% confidence intervals. (From Van den Berghe, 2002).

**Risks**

Because insulin therapy is a new treatment option, there are many issues surrounding it. Some argue that the risks of insulin therapy outweigh any benefits. There are many inconsistencies in the literature concerning the benefits and risks of insulin therapy. Some studies have found no difference in mortality and morbidity while a couple of studies have found that insulin therapy can increase mortality. However, factors such as study design and amount of glycemic control must be taken into account when interpreting the results of these studies.

A large, randomized, controlled, multi-center trial was recently conducted, yielding controversial results. The Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) (2009) trial included 6,104 subjects who were
randomly assigned to an intensive or conventional glucose control group. The intensive group had a target blood glucose range of 81 to 108 mg/dL and the conventional group had a target blood glucose range of 180 mg/dL or less. Blood glucose levels were controlled via intravenous infusion of insulin. The conventional group was given insulin only if blood glucose exceeded 180 mg/dL and the insulin was discontinued when blood glucose dropped below 144 mg/dL. The researchers compared the 90-day mortality of the two groups and found that the intensive treatment group had a higher mortality rate, 27.5% compared to 24.9% (95% CI; P=0.02) in the conventional treatment group. They also found no difference between groups in ICU length of stay, development of new organ failure, and days requiring mechanical ventilation (Finfer et al., 2009).

The results of the NICE-SUGAR study are puzzling when compared to the overwhelming evidence discussed previously that insulin therapy is beneficial. The authors of an editorial article (2009) suggested that the higher mortality could be attributed to the tighter glucose control than was used in the previous studies (Inzucchi & Siegel, 2009). In the Van den Berghe 2001 & 2006 trials the conventional group had a target range of <215 mg/dL compared to <180 mg/dL in the NICE-SUGAR trial. The exact cause of death would be helpful in interpreting why there was no difference in development of organ failure. The data concerning duration of normoglycemia would also be helpful in interpreting the results (Inzucchi & Siegel, 2009).

Aside from the results of the NICE-SUGAR study, the main concern with the use of insulin therapy is an increase in the occurrence of hypoglycemic episodes. A meta-analysis, which included 26 different trials and 13,567 patients, reported a six-fold increase in the risk of hypoglycemic events when insulin therapy was used (Griesdale et al., 2009). The NICE-SUGAR researchers found that severe hypoglycemia, defined as blood glucose ≤ 40 mg/dL, was
much more common in the intensive treatment group compared to the conventional treatment group (6.8% vs. 0.5%) (Finfer et al., 2009). In contrast, Krinsley (2004) found no significant difference in the occurrence of severe hypoglycemia before and after implementation of a glucose management protocol, but the incidence of mild hypoglycemia (blood glucose 40-59 mg/dL) increased from 0.54% to 1.02%. Although the occurrence of mild hypoglycemia increased, it did not result in adverse clinical outcomes (Kricksley, 2004). Both Van den Berghe trials noted an increase in hypoglycemia in the intensive treatment group compared to the conventional treatment group (Van den Berghe et al., 2001; Van den Berghe et al., 2006). Furthermore, the mortality of patients who had a hypoglycemic episode was higher in the intensive group than in the conventional group: 66.7% and 46.4%, respectively (Van den Berghe et al., 2006).

Economic Costs of Insulin Therapy

One important consideration in the use of insulin therapy is the financial cost of the treatment. Because insulin therapy can improve patient outcome measures such as renal failure, need for mechanical ventilation, and infection, insulin can reduce patient and hospital costs. One review estimated that the cost of one day of renal replacement therapy is $731, whereas the cost of the dose of insulin used in the Van den Berghe studies for one day is $2.24 (Gearhart & Parbhoo, 2006). Another review reported a study that found that with every 50-mg/dL increase in blood glucose, patient costs increased by $2,824 and hospital costs increased by $1,769 (Campbell, 2007). Krinsley and Jones (2006) conducted an economical analysis of the glucose management protocol instituted by Krinsley (2004). The researchers noted a reduction in ICU length of stay and hospital length of stay, reduction in duration of mechanical ventilation, and decrease in resource utilization, such as laboratory, pharmacy, and diagnostic imaging, after the
protocol was implemented. This resulted in an estimated total savings of $1,339,500 or $1,580 per patient (Krinsley & Jones, 2006).

The low economic cost is another advantage of insulin therapy. Not only is insulin cheap, its preventative effects can save patients and hospitals from spending money on treatments that would have been unnecessary if insulin therapy had been used. If a safe and effective insulin protocol could be put in place everywhere, the savings on healthcare costs would be immense.

Summary and Future Research Needs

Stress hyperglycemia is extremely common among the critically ill. Although hyperglycemia is a normal part of the stress response, it alters glucose metabolism and causes insulin abnormalities, which can ultimately be detrimental to a patient’s health. There is overwhelming evidence that hyperglycemia in the critically ill is associated with increased mortality and morbidity. There is also strong evidence that the use of insulin therapy to return blood glucose levels to the normal range can reduce the risk of death and improve several important patient outcome measures. However, there is some controversy surrounding the efficacy of the treatment. There are still many questions to be answered before insulin therapy can be used in the most effective manner.

One uncertainty surrounding insulin therapy is which subgroups of patients benefit from the treatment and which subgroups may not benefit. For example, Van den Berghe and colleagues (2006) found that only patients requiring three days or longer of intensive care benefited from intensive insulin therapy (Van den Berghe et al., 2006). Conversely, other studies have found a reduction in mortality and morbidity even in patients with shorter stays (Bochicchio et al., 2005; Krinsley, 2004; Toft et al., 2006). A meta-analysis conducted by Griesdale (2009)
found that insulin therapy had no effect on the overall risk of death, but decreased mortality among surgical ICU patients (Griesdale et al., 2009). Further research is needed concerning the effectiveness of insulin therapy across different subpopulations of critically ill patients.

In addition, the optimal level of glycemic control is unknown. There are many studies investigating insulin therapy, all with different target ranges for blood glucose concentrations. More research needs to be done on which particular range produces the greatest reduction in negative outcomes.

It is difficult to tell from the data whether the insulin or normoglycemia is what causes the desired effects of insulin therapy. One study showed that the anti-inflammatory effects of insulin were responsible for a reduction in organ failure and mortality (Hansen, et al., 2003). However, it was demonstrated in a study of rabbits that normoglycemia contributed most to lower mortality rates. The study had two normoglycemic groups and two hyperglycemic groups and within the two groups there were two subgroups that either received insulin or did not. The hyperglycemic mortality rate was 41.4% whereas the normoglycemic mortality rate was 11.1% and insulin made no contribution to mortality (Vanhorebeek, Langouche, & Van den Berghe, 2007). After analysis of the Van den Berghe (2001) study, the researchers determined that blood glucose control and not insulin was statistically responsible for most of the observed benefits of insulin therapy (Langouche & Van den Berghe, 2006). A definite answer to which contributes more will help dictate the correct insulin dose to be given to critically ill patients.

The conflicting evidence surrounding the benefits of insulin therapy and the ambiguity of who benefits the most from the therapy make it difficult to make any detailed conclusions. Based on the evidence that is available, the author concludes that insulin therapy is safe to use, and most likely advantageous, when blood glucose exceeds 200 mg/dL in critically ill patients.
However, the use of more strict glucose control requires further research before it can be safely used. Currently, it is not possible to determine what specific glucose concentration should be set as the target range when using insulin therapy. Some studies have implemented successful glucose management protocols, but no universal recommendation can be made on which protocol should be used, if any, in all institutions. Individual institutions should determine the details of glucose management protocols. This should be done based on the type of ICU sub-populations being treated. Nurse-to-patient ratios should also be taken into consideration in order to ensure the needs of patients are met with realistic guidelines. The main goal of insulin therapy should be to prevent the adverse effects associated with stress hyperglycemia and to improve overall patient outcome.
References


