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## Glycemic control in the critically ill - How sweet it is

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The acute stress and injury that occurs in association with a critical illness results in a homeostatic response orchestrated by systemic metabolic and hormonal reactions. In a study of septic ICU patients who were not receiving nutritional support, the average plasma glucose was 10.7 mmol/L. In trauma patients from the same institution, plasma glucose was a mean of 9.1 mmol/L, despite similar injury severity scores.<sup>1</sup> Both populations had average glucose levels that were significantly higher than in uninjured fasting controls. During the immediate postoperative period after orthotopic liver transplantation, hyperglycemia was present in almost all patients, but subsided below 11.1 mmol/L within 12 hours.<sup>2</sup>

This rise in blood glucose was viewed as an adaptive response characterized by the production of counter-regulatory hormones such as glucagon, catecholamines, and cortisol. The net result is a state of relative insulin resistance leading to increased liver production of glucose. As a result, glucose is available for use, particularly in insulin-independent tissues such as the brain, inflammatory cells, kidney, and wounds.<sup>3</sup> More recently, investigators have suggested that this hyperglycemic response may be more pathological than physiological, raising questions as to whether it is merely a marker of the severity of illness or a specific pathophysiological process requiring intervention.

Acute hyperglycemia and insulin resistance are frequently observed in critically ill patients, even when glucose homeostasis has previously been normal. The metabolic and hormonal changes that accompany the stress response of a critical illness results in increased gluconeogenesis, despite abundantly released insulin.<sup>3</sup> Hyperglycemia as a manifestation of the stress response is evident shortly after admission to the ICU and may resolve as the underlying catabolic illness subsides. Indeed, persistent metabolic dysregulation and hyperglycemia can be seen in patients with ongoing systemic inflammatory response syndrome (SIRS).<sup>3</sup>

Acute transient hyperglycemia results in physiologic effects that can be detrimental (Table 1).<sup>4-6</sup> These effects can be demonstrated in subjects without diabetes mellitus, suggesting that they are a direct result of the hyperglycemia, and not necessarily the result of acute or long-standing insulin deficiency. Despite the increase in non-insulin-mediated glucose uptake, serum hyperglycemia frequently occurs due to increases in gluconeogenesis, glycolysis, and post-receptor insulin resistance (Table 2). Although the hyperglycemia frequently seen in critically ill patients may represent an adaptive response (with the purpose of maximizing cellular glucose uptake to meet enhanced demand), there is mounting evidence in several different patient populations that tight control of glycemia in both the acute and chronic setting confers significant benefit by decreasing both morbidity and mortality.



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**Table 1: Adverse effects of hyperglycemia**

- Impaired neutrophil activity
- Decreased gastric motility
- Altered cardiovascular tone
- Procoagulant state
- Enhanced inflammatory response

### Effect of insulin on coagulation

The favourable effects of insulin may extend beyond its favourable effects on glucose levels and cellular metabolic functions. Insulin may also confer benefit by reducing plasminogen activator inhibitor-1 (PAI-1) or increasing antithrombin (AT), and/or decreasing IL-6 levels in patients with SIRS, thereby preventing the development of multisystem organ failure (MSOF). Elevated PAI-1, lower AT, and higher IL-6 levels may be associated with insulin resistance and contribute to the higher rates of infection, morbidity, and mortality in these patients. Experimentally, however, acute insulin administration has revealed conflicting results. In a study of patients in the euglycemic hyperinsulinemic state, Landin et al demonstrated a decrease in PAI-1 and an increase in tPA levels,<sup>7</sup> while other investigators have shown that insulin administration has no effect on PAI-1 levels.<sup>8,9</sup> It is important to keep in mind that these studies evaluated acute hyperinsulinemia lasting no more than 48 hours. Thus, the effect of chronic exogenous insulin administration is not yet known. However, the discrepancy is thought to reflect two principles.

- First, the effect of hyperinsulinemia is different in acute versus chronic settings.
- Second, insulin concentration in the portal vein reaching the liver is different from insulin administered peripherally.

In addition, acute peripheral insulin administration is thought to trigger the fibrinolytic system by activating the catecholamine system.

Acute hyperglycemia induced experimentally in a group of type 1 diabetic patients caused an increase in FPA (fibrinopeptide A, a marker of fibrinogen activation) and F<sub>1+2</sub> (a marker of thrombin activation) and a decrease in AT III. Concomitant administration of insulin to prevent hyperglycemia inhibited these changes.<sup>10</sup>

### SIRS-sepsis and inflammatory cytokines

Apart from the deleterious effects of hyperglycemia on the coagulation system, other unfavourable consequences have been identified. Alveolar macrophages and neutrophils exhibit impaired function when exposed to hyperglycemia *in vitro*.<sup>11</sup> As a consequence, the incidence of

**Table 2: Causes of increased serum glucose in critically ill patients**

#### Increased production

- Increase in counter-regulatory hormones
  - Glucagon
  - Epinephrine
  - Cortisol
  - Growth hormone
  - Insulin-like growth factor
- Exogenous catecholamine infusions
- Increased glycolysis
- Increase in hepatic glucose production
- Increase in renal glucose production
- Accelerated gluconeogenesis from other substrates
  - Alanine
  - Lactate
  - Lipolysis
- Iatrogenic hyperglycemia

#### Decreased production

- Reduction in insulin-mediated glucose uptake
- Insulin resistance in tissues
  - Skeletal
  - Cardiac
  - Adipose
  - Liver

postoperative infection is significantly increased in patients with hyperglycemia, diabetes, or both. Cytokines involved in the acute phase reaction are also elevated in patients admitted to the intensive care unit (ICU). The most studied cytokines are tumour necrosis factor (TNF $\alpha$ ) and interleukin-6 (IL-6). Increased TNF $\alpha$  and IL-6 levels have been associated with severity of disease, specifically the presence of sepsis.<sup>12</sup> Levels of these cytokines have also been used as prognostic indicators.<sup>13</sup> Admission and daily TNF $\alpha$  and IL6 levels have been shown to be significantly higher in non-survivors as compared to survivors of SIRS and sepsis.<sup>14</sup> Increased TNF $\alpha$  and IL6 have been shown to correlate with coagulation activation. They are released by macrophages in response to endotoxin. These cytokines cause endothelial dysfunction, activate the coagulation system and fibrin deposition, and can cause myocardial dysfunction.<sup>15</sup> TNF $\alpha$  and IL-6 cause insulin resistance in liver and skeletal muscle.

### The effect of insulin on inflammation

There is strong evidence from *in vitro* and animal studies that insulin can directly decrease TNF $\alpha$  production.<sup>16</sup> Exogenous insulin injection inhibits TNF $\alpha$  production. Animal experiments in rats and canines have shown that the severity of multiorgan failure induced by exogenous TNF $\alpha$  administration is decreased dramatically by concomitant insulin administration.<sup>17</sup>

## Glycemic control in the critically ill – The clinical evidence

### *Infection*

The susceptibility to infection in patients with diabetes is well-established. Several studies have examined the link between perioperative hyperglycemia and post-operative infectious complications in diabetic populations. Post-operative wound infections are significantly increased in patients with hyperglycemia, diabetes, or both.<sup>18</sup> In a comparison of diabetic and nondiabetic patients undergoing coronary artery bypass grafting (CABG), rates of wound infection were significantly higher in the diabetic patients (7.5% versus 0.9%). In studies of diabetic patients undergoing open heart surgery, titration of insulin to maintain blood glucose levels between 8 and 11 mmol/L have been associated with decreased sternal wound infections and improved neutrophil function. In one observational study, in which glucose control was handled entirely by the patients' physicians and surgeons, hyperglycemia (>12.2 mmol/L) on postoperative day 1 was associated with a >5-fold increase in serious infections.<sup>19</sup> In another study involving diabetic patients undergoing CABG, mean post-operative glucose was measured.<sup>20</sup> After adjustment for multiple confounding variables, patients in successively higher quartiles of average blood glucose had progressively higher rates of leg and chest wound infections, pneumonia, and urinary tract infections. It is unclear from these studies whether stress hyperglycemia itself is a risk factor for the infectious complications observed in these patients, independent of the severity of underlying diabetes.

Is stress hyperglycemia – in the absence of underlying diabetes – associated with an increased risk for infectious complications? Alveolar macrophages from normal hosts demonstrate impaired respiratory burst when exposed to elevated glucose concentrations. There is extensive literature detailing the deleterious effects of hyperglycemia on leukocyte and immune system function and it is likely that the effects of stress hyperglycemia are similar to that of actual diabetes.<sup>21</sup> In retrospective studies of burn patients, lower infection rates, improved skin graft success, and lower mortality were associated with insulin therapy titrated to maintain glucose levels below 7.8 mmol/L.<sup>22,23</sup> In a postoperative ICU population, a large randomized controlled trial (RCT) of intensive insulin therapy to maintain blood glucose between 4.4 mmol/L and 6.1 mmol/L demonstrated a 46% reduction in the incidence of blood stream infections.<sup>24</sup>

### *Stroke*

Hyperglycemia is associated with a worse prognosis in patients suffering focal and global cerebral ischemia.<sup>25</sup>

Admission hyperglycemia has also been associated with significant functional impairment after stroke and a 3-fold increase in mortality. In one study, hyperglycemia was an independent predictor of outcome from stroke, after controlling for type and severity of insult.<sup>26</sup> In another observational study, high blood glucose levels on admission were associated with a worse outcome at 3 months after adjustment for stroke size, diabetes, and age.<sup>27</sup> In a pilot study, a glucose/insulin/potassium infusion to return glycemia to a normal level was implemented in an RCT of 53 patients with acute stroke.<sup>28</sup> The results revealed that glucose levels were only slightly lower in the experimental group and that 4-week mortality did not improve. Unfortunately, this study did not answer the question about whether intensification of glycemic control improves outcome in patients with acute stroke due to the lack of significant power and the fact that the mean plasma glucose level at randomization was 8.1 mmol/L in the entire group. A large RCT in this patient population has not been done. Thus, with regard to stroke, the importance of tight glycemic control as a factor influencing outcome is currently unknown.

### *Intracerebral hemorrhage*

Observational studies in patients suffering from intracerebral hemorrhage have identified an association between hyperglycemia and outcome. In one study, elevated plasma glucose levels were associated with higher mortality only in persons who had suffered an intracerebral hemorrhage, but not an ischemic stroke.<sup>29</sup> In addition, stress hyperglycemia, but not pre-existing diabetes mellitus, was a risk factor for mortality in spite of similar blood glucose values. This finding suggests that it is the severity of the clinical condition giving rise to the stress hyperglycemia, rather than the magnitude of the glucose level, that is important for prognosis. A link between hyperglycemia and hemorrhagic transformation of an ischemic stroke after tissue plasminogen activator (tPA) treatment has been demonstrated. In a retrospective evaluation of outcomes in a trial of tPA in stroke patients, baseline serum glucose was the only independent predictor of hemorrhagic transformation. The overall rate of symptomatic bleeds was 25% in patients with serum glucose >11.1 mmol/L, versus only 9% in the normoglycemic patients. Other risk factors such as age, severity of stroke, and computed tomographic scan appearance were significantly less predictive than glucose level.<sup>30</sup>

### *Head injury*

Studies of patients with head injury have similarly demonstrated that admission hyperglycemia in patients without diabetes is associated with a worse outcome.

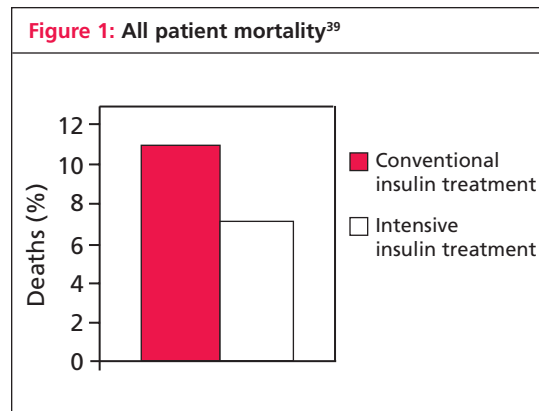
Admission or peak plasma glucose is frequently inversely related to the Glasgow Coma Scale (GCS) score and, in one study, was a predictor of both early and late mortality, irrespective of the presence of multiple injuries.<sup>31</sup> In another study, admission blood glucose was associated with plasma levels of epinephrine and norepinephrine, and mortality was dramatically higher in patients with glucose levels >9.5 mmol/L.<sup>32</sup> A prospective study of patients admitted with traumatic brain injury demonstrated that an admission glucose of >11.1 mmol/L was associated with a poor outcome.<sup>33</sup> There are no published studies examining the effects of normalization of elevated glucose values on neurologic morbidity and overall mortality. In the absence of such data, it is impossible to discern whether stress hyperglycemia in head-injured patients is an epiphenomenon related to the intensity of the counter-regulatory response or an independent predictor of clinical outcome.

### **Myocardial ischemia**

Stress hyperglycemia has been associated with a worse outcome following acute myocardial infarction (AMI). Several observational studies of patients with AMI have demonstrated an association between high admission glucose levels and late mortality.<sup>34-36</sup> Plasma glucose levels on admission in nondiabetic patients with AMI have been shown to be an independent predictor of non-fatal re-infarction, hospital admission for heart failure, and recurrence of a major cardiovascular event.<sup>36</sup>

A systematic review of the effects of stress hyperglycemia on the risk of death after MI was recently published. Patients with admission blood glucose concentrations of >8.1 mmol/L had a 3.9-fold increased risk of death compared to those with lower glucose concentrations.<sup>34</sup> In patients with diabetes and AMI, insulin titration to keep blood glucose levels <11 mmol/L was associated with a significant improvement in outcome.

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial enrolled patients presenting with AMI who also had either diabetes mellitus or hyperglycemia on admission.<sup>37,38</sup> Patients were randomized to either tight control (which involved insulin infusions for 24 hours with the goal of maintaining plasma glucose levels in the range of 7.0 mmol/L to 11.1 mmol/L, followed by multiple daily insulin injections), or to usual care. Average follow-up was 3.4 years, during which a significant mortality benefit was realized in the insulin-treated group.



### **The mortality benefit of euglycemia in postsurgical ICU patients**

Recently, a study by van den Berghe et al demonstrated that intensive insulin treatment and blood glucose control in critically ill patients decreases mortality after admission to the ICU by 42%.<sup>24</sup> This study was conducted mainly in a surgical ICU. Interestingly, the majority of the patients did not have a prior diagnosis of diabetes. In the intensive insulin treatment group, insulin was given to keep glucose levels between 4.4 mmol/L and 6.1 mmol/L during the ICU stay. The conventional treatment group was started on insulin once their blood glucose level exceeded 11.8 mmol/L; their glucose levels were kept between 10 mmol/L and 11.1 mmol/L. Once discharged from the ICU, both groups were treated in a conventional manner. The decrease in mortality in the intensive insulin treatment group (Figure 1) was attributed to decreases in the rates of renal failure, ICU polyneuropathy, sepsis, days requiring mechanical ventilation, need for blood transfusion, and need for antibiotics.

The authors suggest that this was secondary to a decreased frequency of bacteremia and sepsis in the intensive insulin therapy treatment group. Several hypotheses to explain the beneficial effects of insulin were discussed by the authors. For example, the anabolic effects of insulin on respiratory muscles and mucosal barriers, the prevention of the deleterious effects of hyperglycemia on neutrophils and macrophages, and the enhanced erythropoiesis by insulin were put forward as possible mechanisms. Van den Berghe and colleagues further suggest that normalized blood glucose levels, rather than the amount of insulin infused, accounted for the improvement in morbidity and mortality.<sup>39</sup> Nevertheless, the mechanisms underlying the beneficial effects of intensive insulin therapy in acutely ill patients remain unclear.

## Glycemic control in the critically ill – What next?

### *The mortality benefit in severely ill mixed ICU populations is unclear*

The results obtained by Dr. van den Berghe and colleagues suggest that the institution of intensive insulin therapy in mechanically-ventilated, surgical, critically ill adults would improve their outcome. However, these findings cannot be extrapolated to nonsurgical acutely ill patients. The patient population studied in the van den Berghe trial differed substantially from the typical populations found in North American ICUs. The average APACHE II score (a composite measurement of illness) was 9, dramatically lower than most tertiary care units in Canada (whose average APACHE II scores are often 20 or higher). Furthermore, the patients in the van den Berghe trial were disproportionately postcardiac surgery patients (63% of all patients). It is not clear whether the benefit of strict euglycemia would extend to a sicker cohort of patients or to patients whose disease is primarily non-cardiac in nature. Therefore, a confirmatory, multicentre, randomized controlled trial must be performed that includes both surgical and medical ICU patients.

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## Abstract of Interest

### Intensive insulin therapy in critically ill patients.

VAN DEN BERGHE G, WOUTERS P, WEEKERS F, ET AL, LEUVEN, BELGIUM.

**BACKGROUND:** Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

**METHODS:** We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter [4.4 and 6.1 mmol per liter]) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter [11.9 mmol per liter] and maintenance of glucose at a level between 180 and 200 mg per deciliter [10.0 and 11.1 mmol per liter]).

**RESULTS:** At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent ( $P < 0.04$ , with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy,  $P = 0.005$ ). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.

**CONCLUSIONS:** Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.

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