

## Glycemic Control in the Intensive Care Unit and during the Postoperative Period

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**B**OTH critical illness and postoperative status are associated with so-called stress-induced hyperglycemia, defined as transient hyperglycemia during illness in patients without previous evidence of diabetes mellitus.<sup>1</sup> The relationship between stress hyperglycemia and poor outcome is largely established for both conditions. In 2001, a large randomized controlled trial (RCT)<sup>2</sup> in critically ill surgical patients demonstrated that tight glucose control (TGC) (defined as the restoration and maintenance of blood glucose concentration [BG] between 4.4 and 6.1 mM) by intensive insulin therapy (IIT) was associated with a decreased mortality and rate of complications. However, subsequent studies<sup>3–8</sup> performed in other intensive care units (ICUs) failed to reproduce the beneficial effects of IIT.

These conflicting results raise the following clinically relevant question: How can glycemia be controlled in ICUs and during the perioperative period? This commentary summarizes the current understanding of the physiologic regulation

of glycemia, the toxicity of hyperglycemia, the mechanisms and consequences of stress hyperglycemia, and the available clinical data from observational and interventional studies. In addition, the unsolved issues and implications for daily clinical practice will be discussed. Updated formal recommendations will be suggested for glucose control in critically ill and postoperative patients.

### Physiologic Regulation of BG

BG is tightly regulated by the following two types of mechanisms<sup>1</sup>: (1) the *hormonal* system, which consists of a balance between the hypoglycemic insulin hyperglycemic counterregulatory hormones (*i.e.*, glucagon, epinephrine, and cortisol); and (2) the *neural* mechanism, which consists of the activation of messages issued from glucose sensors of various organs.

These hormonal and neural signals modulate carbohydrate metabolism by controlling glucose fluxes, including endogenous production and the entrance of glucose into the cells. The translocation of glucose transporters (GLUTs) is the prominent mechanism for the modulation of glucose transport across cell membranes.<sup>9</sup> Among those transporters, GLUT 1 is the predominant transporter for non-insulin-mediated glucose uptake (fig. 1). GLUT 2 regulates the flow of glucose across liver cell membranes. GLUT 4 is the main insulin-responsive GLUT and therefore modulates the insulin-mediated glucose uptake in adipose tissue and cardiac and skeletal muscles. Some lipids, including ceramides, can interfere with the reading of the GLUT transporter-4 gene and the translocation of the protein to the membrane.<sup>10</sup> This mechanism of insulin resistance can represent a target for future treatment.<sup>10</sup>

### Toxicity Associated with High Glucose Concentrations

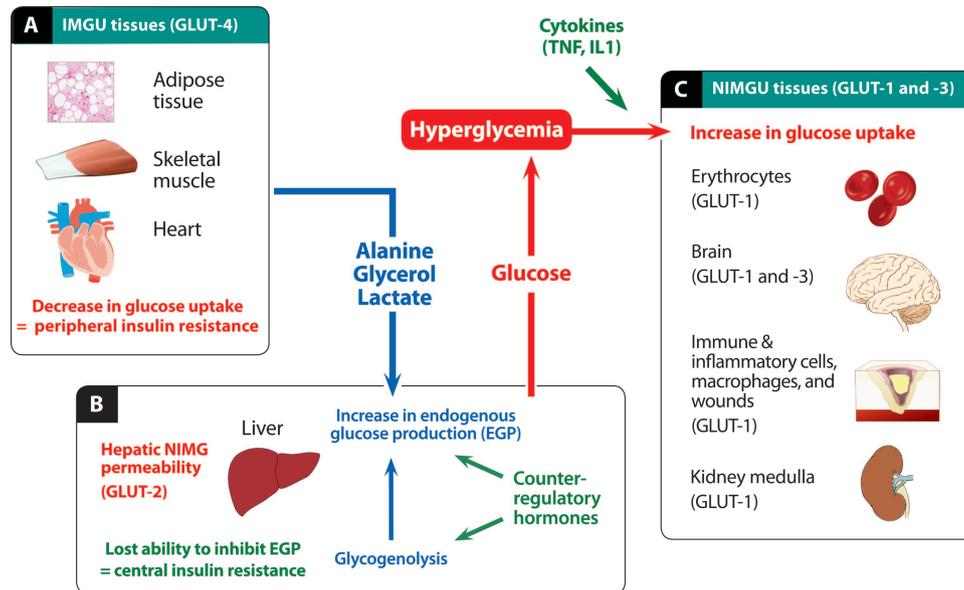
Because glucose is the preferential substrate during critically ill conditions, stress hyperglycemia was considered for a long time as a beneficial response, allowing an adequate provision of energy to tissues. However, in stress conditions, an overall massive glucose overload happens in non-insulin-mediated

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**Fig. 1.** Schematic representation of stress hyperglycemia. (A) In stress conditions, tissues that absorb glucose under the influence of insulin (insulin-mediated glucose uptake [IMGU]) become resistant to the effects of insulin (peripheral insulin resistance). Consequently, glucose is diverted away from IMGU tissues, and neoglucogenic substrates (*i.e.*, alanine, glycerol, and lactate) are released and used by the liver to produce glucose. (B) In the liver, endogenous glucose production is fueled by glycogenolysis and neoglucogenesis, both stimulated by the counterregulatory hormones and less inhibitable by circulating glucose (central insulin resistance). (C) The resulting hyperglycemia finally leads to increased non-insulin-mediated glucose uptake (NIMGU) tissues, under the influence of proinflammatory cytokines. EGP = endogenous glucose production; GLUT = glucose transporters; IL = interleukin; TNF = tumor necrosis factor.

glucose uptake tissues. This accumulation results from the inhibition of the down-regulation of GLUT 1 transporters by proinflammatory mediators, counterregulatory hormones, and hypoxia. Several deleterious effects have been associated with these high glucose concentrations in cells.<sup>1,9</sup> Damages to mitochondrial proteins occur, and the formation of reactive oxygen species is increased as a consequence of the shift from glycolysis toward accessory metabolic pathways (*i.e.*, pentose phosphate, hexosamines, and polyols). Other effects of excess glucose concentrations include the exacerbation of inflammatory pathways, decreased complement activity, modifications in the innate immune system, impairment in endothelial and hepatic mitochondrial functions, abolishment of ischemic preconditioning, and protein glycosylation.<sup>11</sup>

### Mechanisms of Stress Hyperglycemia

Although sharing some similarities, the pathogenetic mechanisms of type 2 diabetes and stress hyperglycemia are different. In diabetes, the cause of hyperglycemia is a combination of insulin resistance and defective secretion by pancreatic  $\beta$ -cells. During stress hyperglycemia, complex interactions between counterregulatory hormones (*e.g.*, catecholamines, growth hormone, and cortisol) and cytokines lead to excessive hepatic glucose production and peripheral insulin resistance (fig. 1). This highly complex interplay is largely variable over time.<sup>1,12</sup>

The increase in hepatic output of glucose results from gluconeogenesis and, to a lesser extent, from glycogenolysis.

Gluconeogenesis is triggered to a larger extent by glucagon than by epinephrine and cortisol. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol. Tumor necrosis factor  $\alpha$  might promote neoglucogenesis by stimulating glucagon production. The increase in peripheral resistance is characterized by the inability of skeletal muscles and adipocytes to absorb glucose, related to an alteration of insulin signaling and down-regulation of GLUT transporter-4. Central insulin resistance is used to define the decreased ability of insulin to suppress hepatic glucose production and seems less affected than peripheral insulin resistance during stress (fig. 1).

During the perioperative period, increased glucose reabsorption or decreased renal glucose clearance has been reported and likely contributes to hyperglycemia.<sup>13</sup> However, surgical stress itself is the most important trigger, *via* the induction of insulin resistance triggered by cytokines and counterregulatory hormones.<sup>12</sup> The degree of insulin resistance has been related to the magnitude and duration of surgical stress. Preoperative and intraoperative insulin resistance has been related to an increased risk of postoperative complications in cardiac and major abdominal surgery, regardless of the patient's diabetic status.<sup>14-16</sup> Preoperative glucose administration has been associated with decreased BG and insulin resistance in nondiabetic patients undergoing major abdominal surgery.<sup>16</sup> On the contrary, patients receiving glucose solutions postoperatively had higher BG than those receiving non-glucose crystalloid.<sup>17</sup> In diabetic patients, the severity of perioperative insulin resistance may

be related to the quality of preoperative glycemic control.<sup>14</sup> In summary, the reduction of intraoperative insulin resistance could probably decrease the incidence of postoperative complications in major surgery. Thus, we suggest favoring preoperative glucose treatment (oral carbohydrate, if possible, or glucose infusion) while avoiding glucose solutions during the first day after major surgery.<sup>17</sup> In diabetic patients, a preoperative determination of hemoglobin A1c is recommended, permitting the evaluation of the preoperative quality of glycemic equilibrium and the degree of intraoperative insulin resistance.<sup>18</sup> The avoidance of hypothermia, excessive blood losses, a prolonged preoperative fasting period, and prolonged immobilization synergize to reduce preoperative insulin resistance.

Only volatile anesthetics have been considered for their impact on glucose metabolism during anesthesia. In a recent experimental study, Tanaka *et al.*<sup>19</sup> showed that isoflurane was responsible for impaired insulin secretion, leading to altered glucose use.

### Glycemic Control: Observational Clinical Studies

Recent and older observational data in various populations of critically ill patients consistently reported admission hyperglycemia as an independent marker of mortality and morbidity.<sup>20</sup> This relationship was the strongest in patients with acute myocardial infarction, stroke, and cerebral hemorrhage. The beneficial effect of decreasing the BG to lower than 8.0 mM in large populations has been suggested by retrospective analysis of large cohorts of critically ill patients. Consistently, in these series, patients with an average BG lower than this threshold had a better outcome than those with an average BG higher than this threshold.<sup>21,22</sup>

After cardiac surgery, the occurrence of hyperglycemia higher than 10 mM was consistently and independently associated with a significant decrease in both deep sternal wound infections and mortality.<sup>23</sup> A recent before–after study assessing 300 diabetic patients found an improvement in vital outcome after implementation of intraoperative glycemic control followed by 3 days of postoperative glycemic control.<sup>24</sup> Conversely, poor glucose control after cardiac surgery was associated with a worsened outcome.<sup>25</sup>

In a before–after trial performed in patients with aneurysmal subarachnoid hemorrhage, Thiele *et al.*<sup>26</sup> found that the implementation of a tight glycemic control protocol (BG target lower than 6.6 mM) led to a similar in-hospital mortality compared with a control group. However, tight glycemic control was associated with an increased risk of hypoglycemia. This latter event was a significant independent predictive factor of increased mortality. These results support the idea that careful glucose management in these patients as a beneficial effect of TGC could be counterbalanced by harmful hypoglycemic events.

### Glycemic Control: Interventional Clinical Studies

#### Glycemic Control in ICUs

The first large landmark RCT included 1,548 surgical ICU patients (mainly cardiac surgery) randomized to IIT (target BG, 4.4–6.1 mM) or to conventional glycemic management (target BG, 10–11.1 mM).<sup>2</sup> In this study, IIT was associated with a reduction in ICU mortality from 8% to 4.6% and in-hospital mortality from 10.9% to 7.2%. These beneficial effects were even larger in patients who spent longer than 5 days in the ICU. In addition, IIT decreased ICU morbidity, expressed by a decreased incidence of systemic infection, acute renal failure, need for transfusion polyneuropathy, duration of mechanical ventilation, and length of stay in the ICU. The Leuven, Belgium, team performed a second study<sup>3</sup> using a comparable method and objectives in a medical ICU population. Considering the whole cohort of 1,200 patients, no significant decrease of in-hospital mortality in the TGC group *versus* the control group was found, although a benefit was found in those staying a long time. The external validity of the Leuven studies and the optimal BG target were assessed in large single- and multiple-center prospective trials<sup>4–8</sup> of TGC by IIT comparing two ranges of BGs. The design of these trials was similar but not identical (table 1).<sup>27</sup> All trials aimed to compare the effects of insulin therapy dosed to restore and maintain the BG between 4.4 and 6.1 mM. They differed in the target range of BG for the control (non-IIT) group. The Glucontrol<sup>7</sup> and the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation)<sup>8</sup> trials used a target value of 7.8–10.0 mM, whereas both Leuven studies,<sup>2,3</sup> the VISEP study<sup>6</sup> (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis), and two other single-center large-scale trials<sup>4,5</sup> used a target value of 10–11.1 mM.

In the NICE-SUGAR study,<sup>8</sup> IIT was associated with an increased 90-day mortality, whereas in the other confirmatory trials, no difference in the outcome of the two groups was found. As expected, IIT was associated with a 4- to 6-fold increase in the incidence of hypoglycemia (reported in 5–25% of the patients randomized to IIT). This high incidence of hypoglycemia represents the major concern when starting IIT and is the major cause of increased medical and nurse workload. In the VISEP<sup>6</sup> and Glucontrol<sup>7</sup> studies, the rates of hypoglycemia and mortality in patients who experienced at least one such episode (defined as a BG of lower than 2.2 mM) were higher than in patients who did not experience hypoglycemia. In contrast, in both Leuven studies,<sup>2,3</sup> hypoglycemic patients had no detectable differences in outcome compared with patients without any hypoglycemic episodes. This does not exclude the possibility that long-lasting hypoglycemia, with consequent decreases in glucose availability for tissues that are glucose dependent, may be deleterious or even life-threatening. An accurate understanding of

**TABLE 1.** Major Differences between the Seven Major Interventional Studies Evaluating Glycemic Control in ICUs

		Van den Berghe <i>et al.</i> <sup>2</sup>	Van den Berghe <i>et al.</i> <sup>3</sup>	NICE-SUGAR <sup>8</sup>	Preiser <i>et al.</i> <sup>7</sup>	Brunkhorst <i>et al.</i> <sup>6</sup>	De La Rosa <i>et al.</i> <sup>5</sup>	Arabi <i>et al.</i> <sup>4</sup>
Number of eligible patients		1,562	2,110	7,294	1,108	600	812	780
Number of patients included		1,548	1,200	6,022	1,101	488	504	523
Percentage of medical patients		0	100	62.9	40.4	46.9	48.8	83.2
Percentage of surgical / postoperative admissions		96.0	0	37.1	56.1	NA	17.2	16.8
Mean admission APACHE II score		9.0	23.0	21.1	15.0	20.2	15.6	22.8
Percentage of calories given intravenously		87.0	87.0	29.5	27.0	66.0	7.0	7.9
Target control (mM)		10.1-11.1	10.1-11.1	7.8-10.0	7.8-10.0	10.1-11.1	10.1-11.1	10.1-11.1
Target IIT (mM)		4.4-6.1	4.4-6.1	4.4-6.1	4.4-6.1	4.4-6.1	4.4-6.1	4.4-6.1
BG values reached [mM - mean (SD) or median (IQR 25-75)]	Control	8.5+/-1.8	8.5+/-1.7	8.1+/-1.4	7.7+/-1.9	8.4+/-1.8	8.2 (6.8-10)	9.5+/-1.9
	IIT	5.7+/-1.1	6.1+/-1.6	6.6+/-1.4	6.1+/-2.0	6.2+/-1.0	6.5 (5.6-7.8)	6.4+/-1.0
Mortality rate (%)		8.0	26.8	24.9	15.3	35.4	31.2	17.1
Hypoglycemia rate (%)	Control	0.8	3.1	0.5	2.7	4.1	1.7	3.1
	IIT	5.0	18.7	6.8	8.7	17.0	8.5	28.6
Mean amount of insulin infused (U/day)	Control	33	10	17	10	5	12	31
	IIT	71	59	50	43	32	52	71
Percentage of patients treated with insulin	Control	39	70	69	66	74	47	75
	IIT	99	98	97	96	98	97	99
Percentage of patients with preexisting diabetes		13	17	20	18	30	12	40

APACHE II = Acute Physiology and Chronic Health; ICU = intensive care unit; IIT = intensive insulin therapy; IQR = interquartile range; NA = not analyzed; NICE-SUGAR = Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation.

the consequences of hypoglycemia in critically ill patients requires further investigations.

### Glycemic Control in the Perioperative Period

Fewer prospective RCTs of IIT were performed in the perioperative setting than in the ICUs.<sup>28</sup> A recent RCT<sup>29</sup> included 73 diabetic and 371 nondiabetic patients undergoing coronary artery bypass grafting. The researchers focused exclusively on the intraoperative period by comparing a TGC group (BG target, 5–6.1 mM) with a conventional group (BG target, lower than 10 mM). After surgery, BG concentrations were equally controlled in both groups. The results

showed that the exclusive short intraoperative glycemic control did not improve postoperative outcome. In summary, the improvement of postoperative outcome related to perioperative glycemic control in cardiac surgery was found in retrospective studies but not confirmed in a prospective trial.

In a prospective, unblinded, randomized trial including patients undergoing peripheral vascular bypass, Subramanian *et al.*<sup>30</sup> evaluated the impact of perioperative continuous intravenous insulin infusion on postoperative morbidity and mortality. During the first day after surgery, BG concentrations were decreased in the interventional group receiving a continuous insulin infusion (BG target, 5.5–8.25 mM)

compared with the control group receiving an intermittent insulin bolus (BG target, lower than 8.25 mM). There was a significant reduction in postoperative cardiovascular events in the intervention *versus* the control group (3.5% *vs.* 12.3%;  $P = 0.013$ ).

Recently, Lipshutz and Gropper<sup>28</sup> reviewed the evidence for perioperative glycemic control. They conclude that perioperative BG should be maintained at less than 8.25 mM and that perioperative TGC could not be supported for routine clinical practice.

### Glycemic Control in Critically Ill Patients and Postoperative Patients: The Unsolved Issues

The discrepancies between the results of the prospective trials of IIT led to various discussions and speculations. Several variables, including the quality of glucose control assessed by the actual BG value achieved, may influence the effect of IIT on outcome. Sampling site and type of devices can interfere with the determination of glucose concentration, especially in cases of vasoconstriction, arterial hypotension, shock, ischemia, and edema.<sup>31</sup> Arterial blood samples and laboratory measurements (or blood gas analyzer devices) provide the most accurate BG values. Depending on the patient's condition, the impact of glycemic control in the ICU could vary. The underlying condition, type of admission, and preexistence of diabetes can also influence the effects of IIT.<sup>20,32–35</sup>

Furthermore, a high rate of hypoglycemia and high glucose variability were associated with increased mortality in retrospective studies and in subsets of patients of prospective trials. However, causal relationships between the occurrence of hypoglycemia and poor outcome in the ICU are not established. In addition to insulin infusion, other markers of severity (*i.e.*, mechanical ventilation, renal removal therapies, sepsis, and catecholamines) predispose to hypoglycemia in critically ill patients.<sup>36,37</sup> Observational studies<sup>38,39</sup> have reported a clear relationship between poor outcome in critically ill patients and BG variability.

Obviously, several issues are left unsolved, including the optimal BG target, the categories of patients who could benefit from IIT, and the logistical requirements for safe and reliable glucose control. Several technical advances that could improve the quality and safety of glucose control include continuous intravascular glucose monitoring and computerized automated algorithms for insulin infusion. Meanwhile, recommendations for daily practice are needed. In the absence of unequivocal evidence from clinical trials, formal expert recommendations have been issued for hospital diabetic inpatients<sup>18</sup> and critically ill and postoperative patients.<sup>40</sup>

### Main Practical Recommendations for Critically Ill and Postoperative Patients

Formalized recommendations that focused on glycemic control in the perioperative period and in critically ill

patients have been elaborated by an international group of experts.<sup>40</sup> Most of these recommendations are summarized in this paragraph.

#### Glucose Target in ICUs

(1) Avoid severe hyperglycemia (more than 10 mM) in adult ICU patients; a universally acceptable upper limit cannot be specified. (2) TGC should be avoided in an emergency situation. (3) Avoid large variations in glucose concentrations in ICUs. (4) Intravenous insulin is the only medication to be used for glucose control in ICUs.

#### Glucose Control in the Perioperative Period

(1) Minimize postoperative insulin resistance by avoiding hypothermia and bleeding and by the preoperative ingestion of clear fluids containing 50–100 g of carbohydrate until 2 h before surgery, unless contraindicated. (2) Avoid hyperglycemia higher than 10 mM after cardiovascular or complicated surgery, in obese patients, or during emergency procedures. (3) Administer infused intraoperative insulin intravenously and continuously, associated with glycemic monitoring every 30–60 min.

#### Hypoglycemia

(1) A glucose threshold of 2.2 mM is used to define severe hypoglycemia. Early detection and correction of hypoglycemia are needed, even in the absence of clinical signs. (2) Arterial or venous blood samples are more reliable than capillary samples in ICU patients with suspected hypoglycemia; capillary samples often overestimate glucose concentration.

#### Carbohydrate Intake

(1) Hyperglycemia may be decreased by restricting intravenous glucose concentration in critically ill patients. (2) Intravenous insulin infusion by electric syringe pump can be discontinued when the patient has resumed food intake while maintaining glucose monitoring for at least three preprandial controls. (3) The daily energy intake in ICU patients must follow the international recommendations of approximately 25 kcal/kg per day. However, optimal carbohydrate intake has still to be established according to the type, severity of pathology, and delay from onset of disease.

#### Glucose Monitoring

Glucose concentrations should be measured in the laboratory or with a blood gas analyzer device. The preferential order of sampling is as follows: arterial, venous, and capillary. The specifications of the device and paper strips used must be known to interpret BG values and to account for possible interferences.

#### Algorithms and Protocols

A standard protocol for glucose control should be used. A specific route of administration should be used for continuous intravenous insulin infusion. A formal protocol must be

dynamic (determination of insulin delivery rate on the basis of the last glucose measurement) and must include at least recommendations on the use of rapid-action insulin as a continuous infusion by electric syringe pump, on the correction and monitoring procedures for episodes of hypoglycemia. Implements in protocols for glycemic control could be obtained by accounting for carbohydrate intake and using a computer-assisted glucose control protocol. Before implementing a glucose control protocol, time should be devoted to train the staff and to account for the increase in workload.

## Conclusion

The adverse effects of excessive hyperglycemia in critically ill patients are undebatable. Data strongly support that BG should be carefully controlled in these populations. However, the concept of TGC by IIT must be revisited because several large RCTs have shown inconsistent results, revealing **no effect or an increased mortality in the glycemic control** group. Therefore, TGC cannot be used in routine practice regardless of the settings, type of patients, and education of the team. New strategies should be developed to achieve glycemic control with a minimal risk of hypoglycemia and of large glucose variations. More efforts should focus on the **quality of BG measurement** devices and BG monitoring modalities, thanks to a computer-assisted algorithm and education of medical and nursing staff. Until such optimizations, each team must implement its own protocol by considering its technical and human resources.

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