Chapter 8
Stress Hyperglycemia

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Abstract The understanding and management of stress hyperglycemia has dramatically changed since 2001. In addition to the development of insulin resistance, stress hyperglycemia is characterised by a poorly inhibitable endogenous production of glucose leading to a severe hyperglycemia. The toxicity of hyperglycemia have been supported by numerous association studies, which reported strong correlations between the magnitude of hyperglycemia and poor outcome. However, tight glycemic control by intensive insulin therapy has not been improved outcomes in most interventional studies and is currently not recommended.

Before 2001, the hyperglycemia found in most critically ill patients was considered as a component of the stress response [1]. Current understanding was completely changed by the publication of the first Leuven study article in 2001 [2]. This investigation compared an intensive insulin regimen targeting a blood glucose level within the 80–110 mg/dL range with a "conventional" management cohort in which blood glucose was treated only when above 200 mg/dL. Van den Berghe and colleagues found a 4 % decrease in the absolute mortality of critically ill patients randomized to intensive insulin therapy. These unexpectedly impressive results triggered a huge wave of enthusiasm. Recommendations to implement tight glucose control in intensive care units (ICUs) were rapidly issued by several healthcare agencies (the Joint Commission on Accreditation of Healthcare Organization, the Institute for Healthcare Improvement, and the Volunteer Hospital Organization). Simultaneously, several different teams tried to reproduce the results and to examine the underlying mechanisms of the findings of the Leuven team. Overall, the results

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of the Leuven study have not been reproduced [3–11]. Nonetheless, these follow-up studies have given rise to several controversies, shed light on the pathophysiology of stress hyperglycemia, and raised important but as yet unanswered questions for the physicians taking care of critically ill patients, including the optimal value of blood glucose, the risks associated with hypoglycemia, and the categories of patient might benefit from tight glucose control by intensive insulin therapy.

8.1 Pathophysiology

It has long been recognized that critically ill patients tend to be hyperglycemic [1]. For many years, this was attributed to stress and was believed to be a part of the adaptive host response to critical illness and designed to provide high amounts of glucose to white blood cells and other obligatory glucose users. Because the blood supply to injured tissue often has been interrupted or diminished, delivery is primarily through mass action across the intracellular matrix. Thus, hyperglycemia was believed to be a biomarker of the severity of illness. The Leuven studies [2, 3] started with the hypothesis that hyperglycemia was not just a biomarker. Rather, these investigators postulated that elevations in serum glucose contributed to the pathophysiology of critical illness. This proposal spawned the current field of investigation.

The physiology behind "stress hyperglycemia" is very different from type II diabetes (Table 8.1). In type II diabetes, the cause of hyperglycemia is a combination of insulin resistance and defective secretion of insulin by pancreatic β-cells. During stress

Table 8.1 Main differences between type II diabetes and stress hyperglycemia

	Diabetes	Stress hyperglycemia
Etiology	Combination of lifestyle and genetic factors	Secondary to trauma, surgery or acute illness
Glycosylated hemoglobin	Elevated if poorly controlled	Normal
Pathogenetic mechanisms	Insulin resistance Defective secretion of insulin (by pancreatic â-cells)	Interaction of regulatory hormones, cytokines Production of glucose by the liver Insulin resistance (IMGU tissues)
Causes of hypoglycemic episodes	Oral medications Insulin	Insulin therapy Interruption of carbohydrates infusion Severe sepsis, liver failure, adrenal insufficiency
Complications	Micro- and macroangiopathy (renal, cardiac, ocular, cerebral, and neurological)	Rather: *complications* related to 1° condition causing dysglycemia
Evolution	Chronic Not curable	Can disappear after resolution of acute illness Higher risk to develop type 2 diabetes
Treatment	Lifestyle Oral medications Insulin (added to oral medication when insufficient)	Treatment of underlying cause Insulin therapy

hyperglycemia, complex interactions between counter-regulatory hormones and cytokines lead to an excessive and non-inhibitable production of glucose associated with insulin resistance of the tissues where glucose uptake is insulin dependent (IMGU), perhaps as an adaptive response needed to promote survival during the acute phase [10, 11]. Indeed, this highly complex interplay is largely variable over time [1, 13].

The stress-related increase in hepatic output of glucose results from glycogenolysis and gluconeogenesis. Glycogenolysis is primarily triggered by catecholamines and perpetuated under the influence of epinephrine and cortisol. Gluconeogenesis is triggered to a larger extent by glucagon than by epinephrine and cortisol. Among the numerous inflammatory mediators released in the acutely ill, tumor necrosis factor-α (TNF-α) might promote gluconeogenesis by stimulating glucagon production. The increase in peripheral resistance is characterized by the inability of skeletal muscles and adipocytes to take up glucose, related to an alteration of insulin signaling and with a downregulation of type 4 glucose transporters (GLUT-4).

An increased glucose reabsorption or a decreased renal glucose clearance has also been reported and likely contribute to hyperglycemia in acute conditions [15]. In the postoperative patient, the surgical stress itself is an important trigger, via the induction of insulin resistance under the influence of cytokines and counter-regulatory hormones. The degree of insulin resistance has been related to the magnitude and the duration of the surgical stress. The avoidance of hypothermia, excessive blood losses, prolonged preoperative fasting period, and prolonged immobilization synergize to reduce perioperative insulin resistance.

8.2 Toxicity

In experimental conditions, concentrations of glucose higher than 300 mg/dL are clearly deleterious. New insights into the cellular mechanisms of glucose toxicity suggest a link among glucose, cytopathic hypoxia, and the production of reactive oxygen and nitrogen species [10, 13, 14]. However, the optimal blood glucose target is undefined yet and could differ according to the underlying condition, including the preexistence and the control of diabetes. Likewise, the ultimate proof that hyperglycemia is an independent risk factor for poor outcome in critically ill patients is lacking. Importantly, insulin exerts effects other than the promotion of glucose metabolism and utilization. These include vasodilatory, anti-inflammatory, and anti-apoptotic activities that can be viewed as a homeostatic control mechanism limiting some of the processes that occur in inflammation and other potentially injurious responses. The non-glycemic effects of insulin might also explain some of the beneficial effects of intensive insulin therapy.

In stress conditions, an overall massive glucose overload happens in organs where glucose uptake is not regulated by insulin, usually quoted as NIMGU (*non-insulin-mediated glucose uptake*) tissues under the influence of pro-inflammatory mediators, counter-regulatory hormones, and hypoxia [10]. Hence, a wide range of tissues, including hepatocytes, endothelial cells, neurons, nephrons, and immune cells, may be susceptible to enhanced glucose toxicity as a result of acute illness.

Several deleterious effects have been associated with these high glucose concentrations in cells [1, 12]. Damages to mitochondrial proteins occur, and the formation of reactive oxygen species (ROS) is increased as a consequence of the shift from glycolysis toward accessory metabolic pathways (pentose phosphate, hexosamines, polyols) [13]. 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 the ischemic preconditioning, and protein glycosylation. Acute complications attributed to stress hyperglycemia include renal failure, increased susceptibility to infections and polyneuropathy, and impaired microcirculation [1].

8.3 Clinical Associations Between Hyperglycemia and Poor Outcome

Quite consistently, retrospective studies performed on large cohorts of different categories of critically ill patients reported poorer outcome of patients who experienced dysglycemic events. However, the strength of the relationship between markers of dysglycemia and outcome is variable according to the diabetic status. Overall, admission hyperglycemia was found as an independent marker of mortality and morbidity [16–20].

After cardiac surgery, the occurrence of hyperglycemia 180 mg/dl was consistently and independently associated with a significant increase in both deep sternal wound infections and mortality [20–22].

Comparing the relationship between dysglycemia and outcome in diabetic and nondiabetic critically ill patients yielded interesting and consistent differences. Several studies consistently reported a flatter relationship or J-shaped curve between BG and mortality in diabetic than in nondiabetic patients [23–28].

8.4 Conclusions

A consistent and clear association between hyperglycemia and poor outcome is present in critically ill patients. These findings support the current recommendation of liberal glucose control by insulin, namely, in view of the risks associated with tighter therapeutic strategies [29–31]. The use of consistent indices of the three domains of dysglycemia (hyperglycemia, hypoglycemia, and high glycemic variability) is required to delineate the optimal BG target in different categories of patients, the logistical requirements for a safe and reliable glucose control, and to assess technical advances that could improve the quality and safety of glucose control [32].

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