Dysglycemia and Glucose Control During Sepsis

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KEYWORDS

• Sepsis • Hyperglycemia • Hypoglycemia • Glycemic variability

KEY POINTS

- The 3 domains of sepsis-induced dysglycemia, hyperglycemia, hypoglycemia, and glycemic variability, occur frequently in patients with sepsis and are associated with increased mortality.
- Dysglycemia may not represent the same insult to all septic patients and may be altered by patients' long-term blood glucose control.
- Future randomized controlled trials should consider all 3 domains of dysglycemia as important outcomes with variable associations with mortality based on premorbid glycemic control.

INTRODUCTION

The physiologic stress of sepsis results in marked disturbances in metabolism and glucose regulation. Disordered metabolism can be divided into 3 separate but interrelated categories, otherwise known as 3 domains of critical illness dysglycemia, which are hyperglycemia, hypoglycemia, and glycemic variability.[1–3] These dysglycemic states occur frequently, with the prevalence of hypoglycemia and hyperglycemia increasing along the continuum from sepsis through severe sepsis and septic shock.[4] Although hyperglycemia, hypoglycemia, and glycemic variability are all associated with increased mortality,[2,3,5] the management goals of patients with sepsis and hyperglycemia remain contentious. This review focuses on the relevance of the 3 domains of dysglycemia in septic patients, with particular emphasis on a rational approach to blood glucose management.

DEFINITIONS, PREVALENCE, AND PATHOGENESIS

Hyperglycemia occurs frequently in patients who are critically ill due to sepsis and is a marker of illness severity.[6] Many of these patients have previously been diagnosed with diabetes mellitus. A smaller proportion of patients may have diabetes that was unrecognized before the onset of sepsis. Furthermore, patients may have hyperglycemia in the absence of preexisting glucose intolerance (whether diagnosed or not), so-called stress hyperglycemia. The distinction between these clinical entities is important as recent retrospective and prospective observational data indicate that the association between hyperglycemia and mortality may be modulated by patients' chronic glycemic state.[7–10]

Stress Hyperglycemia

In the critically ill, the precise threshold blood glucose concentration that causes harm and, therefore, constitutes pathologic hyperglycemia remains controversial. The American Diabetes Association (ADA) Diabetes in Hospitals Writing Committee's guidelines recommend thresholds of fasting glucose greater than 6.9 mmol/L, 124 mg/dL or random glucose greater than 11 mmol/L, and 198 mg/dL[11] as identifying disordered glucose metabolism; but these are based on pathologic thresholds in health.[12] Although these values facilitate standardization in the

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critically ill, the blood glucose thresholds that cause harm are likely more complex in patients with sepsis and may fluctuate throughout an individual patient's illness. Regardless of definitive values, it seems that hyperglycemia occurs frequently in critically ill patients with sepsis, even in those who did not previously have diabetes. The authors prospectively studied 1000 consecutively admitted patients and classified them as having recognized diabetes, unrecognized diabetes, stress hyperglycemia, or normal glucose according to their past medical history, glycated hemoglobin (HbA_{1c}) obtained on admission, and peak blood glucose in the first 48 hours.[10] Patients were deemed to have stress hyperglycemia if their blood glucose exceeded the aforementioned ADA thresholds and HbA_{1c} was less than 6.5% (47.5 mmol/mol). Of the 1000 patients, 67 were admitted with a primary diagnosis of sepsis; in this subgroup, preexisting diabetes (recognized or not) occurred in approximately 45% and stress hyperglycemia in approximately 40% of patients (**Fig. 1**), consistent with the concept that disordered glucose metabolism occurs frequently during sepsis.

Mechanism of Stress-Induced Hyperglycemia

Sepsis-induced hyperglycemia is initiated by the overwhelming activation of proinflammatory mediators and the release of counter-regulatory hormones leading to excessive hepatic gluconeogenesis and peripheral insulin resistance.[13] Cortisol, catecholamines, interleukin-6, tumor necrosis factor-α, and glucagon independently and synergistically stimulate hepatic glucose production with hyperglucagonemia seeming to be of pivotal importance.[13–15] Peripheral insulin resistance is directly proportional to the severity of the stress response[16] and results from defects in postreceptor insulin signaling, with subsequent downregulation of insulin-mediated GLUT-4 glucose transporters.[17] The exact mechanisms whereby sepsis induces defective translocation of GLUT-4 transporters is unclear; however, data from animal studies implicate cortisol,[18] catecholamines,[19] growth hormone,[20] and tumor necrosis factor-α[21] as particularly important. The hyperglycemia attributed to these metabolic derangements is further exacerbated by therapeutic interventions, such as administration of catecholamines, dextrose, corticosteroids, and nutrition.

Harm Secondary to Hyperglycemia

Acute hyperglycemia has been recognized as a marker of the severity of illness.[6,22,23] Moreover, various investigators have repeatedly reported that the magnitude of hyperglycemia is associated with increased mortality, even after adjusting for illness severity scores, suggesting that at some threshold hyperglycemia is harmful in patients with sepsis.[6,22,23] However, recent data from Kaukonen and colleagues[24] suggest the relationship between hyperglycemia and harm may be more complex and the variables used in previous studies to adjust for risk may have been imprecise. In a retrospective observational study of patients' concurrent glucose and lactate samples (n = 7925 critically ill patients), they used multivariable analysis and reported no association between hyperglycemia and mortality once lactate levels were incorporated into the model.[24] These data challenge the causal relationship of hyperglycemia with mortality within the spectrum of moderate-glucose

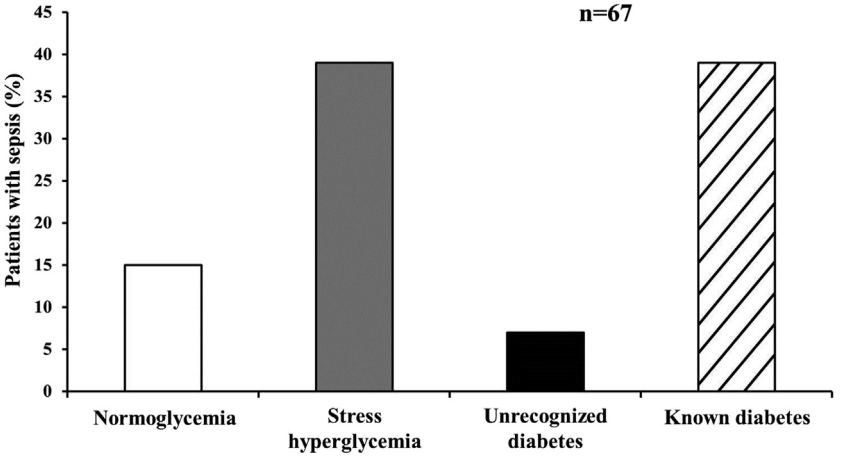

Fig. 1. Glycemic category in critically ill patients with a primary diagnosis of sepsis. In a population of 1000 consecutively admitted patients, there were 67 admitted with a primary diagnosis of sepsis. Most septic patients had preexisting diabetes or stress hyperglycemia.