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Pathophysiology and management strategies for hyperglycemia for patients with acute illness during and following a hospital stay

Nicole C. Dombrowski[a], Dennis G. Karounos[a,b,*]

[a] Division of Endocrinology and Molecular Medicine, University of Kentucky College of Medicine, Lexington, KY
[b] Department of Veterans Affairs Medical Center, Medical Service, Lexington, KY

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ABSTRACT

Hyperglycemia in the inpatient setting is associated with poor clinical outcomes and is often suboptimally managed. This review addresses the pathophysiology of hyperglycemia, current recommendations for management of inpatient hyperglycemia in the general medical and surgical care setting, the transition between different diabetes treatments, and the transition from inpatient to outpatient therapy. The preferred drug for management of inpatient hyperglycemia is insulin. Successful use of intravenous and subcutaneous insulin in the hospital is based on the implementation of standardized protocols. Current guidelines recommend basal-bolus subcutaneous insulin in non-critically ill patients. The methods of switching from intravenous to subcutaneous, sliding-scale to basal-bolus, and biphasic to basal-bolus are discussed. Transition from an inpatient to an outpatient insulin regimen, especially in patients new to insulin therapy, requires special attention to ensure that patients have the knowledge to administer insulin safely and effectively. The optimal regimen at discharge must be individualized. Patients with acute infections may benefit from insulin therapy until the infection is resolved. Strategies to optimize diabetes therapy after discharge are discussed. Prompt outpatient follow-up is crucial to ensure optimal glycemic control. Despite the challenges, improved glycemic control in individuals with acute illness has the potential to reduce morbidity and mortality in individuals with this widespread metabolic illness.

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1. Introduction

Hyperglycemia (defined as a blood glucose [BG] level greater than 140 mg/dL [7.8 mmol/L]) can occur in both diabetic and non-diabetic hospitalized patients [1,2], and is common among acute hospital admissions and critically ill patients, including those with no previous history of hyperglycemia [3,4]. It can result from infection, traumatic injury, and surgical procedures and is also a side effect of some medications, such as corticosteroids, antipsychotics, and antiretroviral therapies [5]. Importantly, inpatient hyperglycemia can increase morbidity and mortality, and is predictive

Abbreviations: ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; BG, blood glucose; GLP-1 agonists, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HPA axis, hypothalamic-pituitary-adrenal axis; IGT, impaired glucose tolerance; IL, interleukin; IV, intravenous; NPH, Neutral Protamine Hagedorn; npo, nothing by mouth; po, orally; sc, subcutaneous; SH, Stress hyperglycemia; SSI, sliding-scale insulin; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α; TPN, total parenteral nutrition; U, unit.

* *Corresponding author*. Tel.: +1 859 323 6584; fax: +1 859 233 3832.
E-mail address: dkaroun@uky.edu (D.G. Karounos).

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of poor outcomes, including length of hospital stay and mortality [6–8]. For example, hyperglycemia increases the risk of infection and predisposes patients to cardiac arrhythmias [5,9,10]. Similarly, data from the Portland Diabetic Project, a 17-year prospective study of over 4800 patients with diabetes who underwent an open-heart surgical procedure, showed that continuous intravenous (IV) insulin therapy in patients with BG levels greater than 150 mg/dL independently reduced the risks of death and deep sternal wound infections by 57% and 66%, respectively (both $p < .0001$) [11]. Indeed, the importance of strict inpatient control of hyperglycemia is well documented as summarized in recent position statements [12–14]. Furthermore, the American Diabetes Association (ADA) guidelines state that in the hospital setting insulin is the preferred therapy for achieving and maintaining glucose control for the majority of clinical settings [12]. Despite these guidelines, inpatient hyperglycemia is often inadequately addressed, both in general medicine and surgical patients [15]. This review addresses the current recommendations for management of inpatient hyperglycemia, the challenges of insulin treatment in the inpatient setting, transitioning between inpatient insulin regimens, and the transition to outpatient care.

2. Pathophysiology of hyperglycemia in hospitalized patients

Hyperglycemia is a frequent and serious problem in acutely ill hospitalized patients. It has been linked to poor outcomes, both in diabetic patients and in patients having no prior history of diabetes [16]. Hyperglycemia induces changes in inflammatory cytokines, blood coagulation, angiogenesis, immune cell function and wound healing. When hyperglycemia occurs during trauma, severe illness or major surgery, it is termed "stress hyperglycemia (SH)" or admission hyperglycemia. While SH is associated with increased mortality rates, several studies suggest that the risks are more pronounced in patients with no pre-existing diabetes. For example, in a study of 1886 unselected hospitalized patients with hyperglycemia, the risk of death was 2.7 times greater for diabetic patients and 18.3 times greater for non-diabetic patients [17]. Hyperglycemia in non-diabetic individuals may be a marker for increased severity of illness. According to the ADA, patients should be stratified into three distinct groups when evaluating SH. Two of the 3 groups are comprised of patients with pre-existing diabetes; for these patients, hyperglycemia diagnosed in the hospital is due to deterioration of prior glycemic control mechanisms. Of these patients, some are known diabetics and some are as-yet-undiagnosed. The third grouping consists of normoglycemic patients experiencing hospital-related hyperglycemia [18]. According to Ishihara et al., "admission hyperglycemia" and type 2 diabetes mellitus (T2DM) should be treated as two distinct diseases [19]. In their study of 802 consecutive patients with acute myocardial infarction who underwent coronary angiography, they found that the thirty day mortality rates were higher in patients presenting with admission hyperglycemia (without a prior diagnosis of diabetes) compared to patients with known diabetes. In contrast, in patients without admission hyperglycemia regardless of diabetes diagnosis status, the thirty day mortality rates were lower. However, in the long-term (thirty days to three years) follow-up after an acute myocardial infarction, patients with known diagnosis of diabetes had a higher mortality than the cohort of patients with the admission hyperglycemia. They concluded that admission hyperglycemia was associated with an increase in short-term mortality while known diabetes was associated with an increase in long-term mortality [19]. Possible mechanisms for this increased mortality include hyperglycemia-induced changes in coagulation, alterations in endothelial function and increases in inflammatory cytokines. Direct evidence to support the latter was provided by Esposito et al., who demonstrated that in normal subjects and individuals with impaired glucose tolerance (IGT), hyperglycemia induces production of inflammatory cytokines interleukin (IL) -6, tumor necrosis factor-α (TNF-α) and IL-18 by an oxidative mechanism [20]. Using an artificial pancreas (Biostator, Life Sciences) they induced acute hyperglycemia by clamping glucose to 15 mmol/L for 5 h while blocking endogenous insulin secretion with octreotide. The inflammatory cytokines increased in response to hyperglycemia in both normal individuals and in the IGT group but the response was greater in the IGT cohort. The cytokine response could be blocked by the infusion of glutathione, suggesting that the hyperglycemic-induced cytokine response occurs by an oxidative mechanism. They also showed that the effects of sustained hyperglycemia could be reproduced by transient oscillations of glucose levels and that this response was greater in individuals with IGT. This may have relevance to individuals with stress hyperglycemia, as these patients may have only transient elevations of blood glucose. The increases in TNF-α may alter insulin-receptor signaling and increase insulin resistance [20]. Thus, elevated blood glucose itself causes an inflammatory response, leading to the production of pro-inflammatory cytokines and reactive oxygen species, which may induce further hyperglycemia [21]. In patients with hyperglycemic crisis without obvious infection or cardiovascular pathology, Stentz and colleagues [21] demonstrated that there is an increase in the proinflammatory cytokines IL-1α, IL-6, IL-8, and TNF-α, and these levels returned to normal after insulin therapy and resolution of the hyperglycemic crisis. The TNF-α levels were higher in obese subjects compared to lean individuals. In addition, cortisol, growth hormone and free fatty acid levels were increased with hyperglycemia and normalized with insulin therapy and resolution of the hyperglycemic crisis. A similar pattern was also seen with markers of cardiovascular risk (C-reactive protein, homocysteine, and plasminogen activator inhibitor-1) and markers of oxidative stress and lipid peroxidation (reactive oxygen species, thiobarbituric acid-reacting material and dichlorofluorescein). The reduction of multiple cytokines, markers of cardiovascular risk and oxidative stress with insulin therapy suggested that insulin therapy has important anti-inflammatory effects [21].