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Impact of Glycemic Variability on Prognosis in Sepsis Patients

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Abstract

Sepsis patients frequently develop metabolic disorders due to the uncontrolled release of inflammatory mediators, leading to significant fluctuations in blood glucose levels and an increased risk of adverse outcomes. Glycemic variability (GV), an indicator reflecting blood glucose fluctuations, is closely associated with mortality in sepsis patients. Studies have demonstrated that 40% - 60% of sepsis patients exhibit hyperglycemia, while severe hyperglycemia (≥200 mg/dL) or low GV (<15.174%) are significantly correlated with an elevated risk of ICU mortality. Blood glucose fluctuations exacerbate organ damage through oxidative stress mechanisms, with labile hyperglycemia more readily activating signaling pathways such as NF-κB and MAPK compared to stable hyperglycemia, thereby promoting inflammatory responses and apoptosis. Furthermore, immune and metabolic dysregulation in sepsis patients further aggravates GV, forming a vicious cycle. Clinical data confirm that elevated GV is positively correlated with all-cause mortality in sepsis patients, whereas stringent control of glycemic fluctuations may improve prognosis. Future research should further explore GV modulation strategies to optimize blood glucose management in sepsis patients and reduce mortality rates.

Keywords

Blood Sugar Variability, Sepsis, Prognosis

1. Introduction

1) Sepsis

Sepsis is a systemic inflammatory response syndrome triggered by infection [1], whose pathophysiological process involves complex immune and metabolic dysregulation. Following pathogen invasion, the host's immune system becomes hyper-

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activated, leading to the massive release of pro-inflammatory cytokines. These inflammatory mediators not only participate in immune defense but also disrupt normal metabolic processes, particularly glucose metabolism. During the early stages of sepsis, the body enters a hypermetabolic state with significantly increased energy demands. To meet these demands, secretion of hyperglycemic hormones increases. These hormones elevate blood glucose levels by promoting hepatic glycogenolysis and gluconeogenesis. Concurrently, inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) can directly act on insulin signaling pathways. They interfere with the phosphorylation of insulin receptor substrates (IRS) and suppress phosphatidylinositol 3-kinase (PI3K) activity, thereby inducing insulin resistance [2]. This state of insulin resistance reduces the ability of peripheral tissues to uptake and utilize glucose, further exacerbating hyperglycemia. As sepsis progresses, persistent inflammation may impair pancreatic β-cell function. Research indicates [3] that IL-1β can activate the nuclear factor κB (NF-κB) pathway, inducing apoptosis in pancreatic β-cells and reducing insulin secretion. Furthermore, hyperglycemia itself exerts toxic effects, creating a vicious cycle: elevated blood glucose promotes the release of inflammatory factors, while inflammation exacerbates insulin resistance and hyperglycemia. This metabolic dysregulation not only compromises energy supply but also induces organ dysfunction through multiple mechanisms. Numerous studies have revealed that septicemia patients exhibit a state of uncontrolled massive release of inflammatory mediators and cytokines, which can elicit metabolic dysregulation and cause significant fluctuations in patients' blood glucose levels [4]. Furthermore, both hyperglycemia and hypoglycemia events in ICU patients will increase the risk of poor prognosis [5]. It has been reported that 40% - 60% of sepsis patients experience hyperglycemic events during hospitalization [6]. In recent years, the role of Glycemic Variability (GV) in critical care has gained increasing attention. Severe septicemia remains a leading cause of mortality in intensive care unit (ICU) patients. Despite continuous improvements in comprehensive treatment protocols in recent years, septicemia patients still face mortality rates as high as 35% to 70%, with suboptimal quality of life [7]. This review summarizes research advances regarding GV in sepsis.

2) Glycemic variability (GV)

Glycemic variability (GV) refers to an indicator reflecting blood glucose fluctuations that exist independently of single-point measurements, representing the range of blood glucose fluctuations over a given period [8]. GV encompasses multiple dimensions: fluctuation amplitude (difference between maximum and minimum glucose values), fluctuation velocity (rate of glucose increase/decrease), fluctuation frequency (number of fluctuations per unit time), and fluctuation pattern (regular/irregular). Currently, no unified standard exists for GV assessment. Eslami *et al.* [9] have identified 12 metrics for assessing GV in critically ill patients. Commonly used evaluation indicators include: a) Standard Deviation (SD): The standard deviation of all blood sugar values for each patient during the ICU, re-

flects the dispersion of blood glucose values around the mean; b) Coefficient of Variation (CV): Blood sugar standard deviation × 100/blood sugar average, the ratio of standard deviation to mean blood glucose, which eliminates the influence of absolute glucose levels; c) Mean Amplitude of Glycemic Excursions (MAGE): Calculate the absolute value of all two adjacent blood glucose differences, and find the average value of those values >1 standard deviation. Calculates only clinically significant fluctuations exceeding a specific threshold; d) Glycemic Lability Index (GLI): Σ(The difference between two adjacent blood sugars/adjacent blood sugar interval)/number of weeks, comprehensively considers both the magnitude of blood glucose fluctuations and temporal factors. In sepsis patients, the assessment of glycemic variability (GV) must also account for the influence of disease severity and therapeutic interventions. Therefore, interpreting GV metrics requires comprehensive analysis within the clinical context. Blood glucose fluctuations encompass both physiological and pathological variations. Physiological fluctuations refer to blood glucose variations under normal conditions, determined by the combined effects of nutrient absorption/utilization levels and insulin secretion, which are maintained within a reasonable and controllable range. Typically, intraday blood glucose fluctuations range between 2 - 3 mmol/L with a frequency of 5 times per day, while interday fluctuations average 0.8 mmol/L [10]. Critically ill patients exhibit diminished capacity to maintain glucose homeostasis due to causative factors such as stress, infection, and surgery, alongside worsening insulin resistance, islet cell dysfunction, and increased secretion of inflammatory factors and hyperglycemic hormones. [11], blood glucose levels gradually rise and fluctuation amplitudes increase significantly compared to healthy individuals. Basic research confirms [12] that pro-inflammatory cytokines such as TNF-α and IL-6 can bind to target cell receptors for insulin action. This not only inhibits glucose transport but also elevates levels of hormones including adrenal corticosteroids and catecholamines, indirectly affecting insulin sensitivity and exerting biological effects of insulin resistance. According to the research by Mercedes F *et al.* [13], when blood glucose exceeds 16.67 mmol/L, the mortality risk in critically ill patients increases 2.85-fold. Hypoglycemia also demonstrates a significant correlation with poor prognosis in critically ill patients. The NICE-SUGAR study revealed that hypoglycemia occurs in 18% to 65% of critically ill patients, with mortality rates among severe hypoglycemia patients reaching 35.4% to 50.2% [14]. A study involving 7104 ICU patients with septicemia indicated that severe hyperglycemia (≥200 mg/dL) and low GV (<15.174%) during ICU hospitalization were significant risk factors for ICU mortality in sepsis patients, regardless of diabetes status. Elevated mean blood glucose levels and increased GV were significantly associated with heightened all-cause mortality in ICU septicemia patients [15]. This study revealed that the impact of glycemic variability (GV) on prognosis follows a U-shaped curve relationship, indicating that both excessively low and high GV levels correlate with poor prognosis. This suggests maintaining appropriate blood glucose stability may be crucial for improving clinical outcomes. To date, no large-

scale clinical studies have established a safe glycemic variability (GV) range for critically ill patients; however, intensive insulin therapy has fallen out of favor [16]. In 2009, the American Diabetes Association (ADA) clinical practice recommendations suggested that for surgical critically ill patients, the target blood glucose range should be close to 6.1 mmol/L and generally maintained below 7.8 mmol/L [17]. For non-surgical critically ill patients, although no specific blood glucose target was defined, maintaining glucose levels between 6.1 and 7.8 mmol/L may reduce complications and mortality. The 2014 ADA Standards of Medical Care in Diabetes recommended initiating insulin therapy in critically ill patients with persistent hyperglycemia exceeding 10 mmol/L [18]. Once insulin therapy is started, it is advised that blood glucose be maintained within the range of 7.8 - 10.0 mmol/L for most patients. The method of glucose monitoring also influences the assessment of GV. Monitoring can be classified into intermittent and continuous glucose monitoring. Intermittent monitoring involves clinicians selecting the frequency of glucose testing—such as every 1 to 8 hours—based on the patient's condition. Glucose values are obtained from capillary blood, peripheral venous blood, or arterial blood. Discrepancies among these blood sources can affect the accuracy of GV evaluation. Previous studies have shown that approximately 15% of capillary blood glucose values may deviate by more than 20% from laboratory-measured venous blood values [19] [20]. Moreover, the frequency of glucose testing, which depends on clinical decisions, may fail to capture substantial glycemic fluctuations. Continuous glucose monitoring systems (CGMS) overcome the limitations of intermittent monitoring by providing a more comprehensive and accurate reflection of glycemic variations. In 2014, a new type of continuous glucose monitoring system—flash glucose monitoring (FGM)—was approved for use in the European Union, marking a revolutionary advancement in glucose monitoring technology [21] [22]. FGM measures glucose levels in interstitial fluid to provide overall glycemic information without the need for fingerstick calibration. By simply scanning the sensor, real-time glucose values can be obtained along with a 14-day continuous glucose profile. This system enables real-time feedback to support clinical decision-making.

2. Factors Affecting the Prognosis

GV influences sepsis prognosis through multiple pathways. First, blood glucose fluctuations exacerbate oxidative stress responses. Second, GV activates inflammatory pathways such as NF-κB and MAPK signaling cascades, further amplifying the inflammatory response. Third, blood glucose fluctuations impair vascular endothelial function and promote microcirculatory dysfunction, which plays a pivotal role in sepsis-associated organ failure. It is particularly noteworthy that the impact of GV may vary across different organ systems. In the cardiovascular system, blood glucose fluctuations exacerbate cardiomyocyte apoptosis and systolic dysfunction; for the kidneys, GV may aggravate acute kidney injury by increasing glomerular endothelial cell permeability; regarding the nervous system,

GV can disrupt the blood-brain barrier, worsening cerebral edema and delirium risk. Collectively, these organ-specific effects contribute to poor prognosis in sepsis patients. The primary mechanism by which blood glucose fluctuations cause organ dysfunction in critically ill patients stems from M Brownlee's 2001 [23] proposed oxidative stress as the unifying mechanism for diabetic chronic complications. Its core lies in the mitochondrial electron transport chain generating various superoxides—such as reactive oxygen species (ROS) and reactive nitrogen species (RNS)—under hyperglycemic conditions [24], which activates signaling pathways including NFκB, mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK). This process induces multiple pro-inflammatory cytokines, ultimately leading to organ dysfunction in critically ill patients [25]. In recent years, research [26] has found that blood glucose fluctuations exacerbate oxidative stress, further inducing inflammatory responses; fluctuating hyperglycemia causes more severe oxidative stress than stable hyperglycemia, accelerating cellular apoptosis and damage. Lisa Q *et al.* [27] demonstrated that in umbilical vein cells, compared to sustained hyperglycemia, intermittent hyperglycemia produces higher levels of protein kinase C-β (a surrogate marker of oxidative stress). In similar experiments, Louis M *et al.* [28] also discovered that blood glucose fluctuations may trigger adverse biological events and oxidative stress in type 2 diabetes patients. Additionally, Hirotaka W *et al.* [29] experimental results also demonstrated that high blood glucose variability in rats enhances monocyte-endothelial cell adhesion. Given the significant impact of GV on sepsis prognosis, optimizing blood glucose management strategies holds substantial clinical importance. Traditional blood glucose control targets primarily focus on absolute values, such as maintaining ICU patients' blood glucose within 6.1 - 8.3 mmol/L. However, mounting evidence suggests that while achieving glycemic targets, reducing GV should also be prioritized.

3. Discuss

Septicemia constitutes a critical condition caused by pyogenic pathogens invading the bloodstream from infection sites and proliferating extensively. With further progression, patients may develop septic shock, severe sepsis, or even multiple organ dysfunction syndrome, resulting in severely compromised quality of life [30]. Patients often experience a sharp reduction in effective circulating blood volume and systemic hypoperfusion of tissues and organs. This state serves as the primary cause of impaired microcirculatory perfusion, imbalance between oxygen supply and demand, and accumulation of metabolic byproducts, ultimately leading to multi-organ dysfunction. [31], representing a clinically common systemic inflammatory response syndrome with high incidence and mortality rates. Severe sepsis has become the third leading cause of death among patients [32]. In recent years, influenced by evolving lifestyles and environmental deterioration, the prevalence of this disease has shown an increasing trend year by year, posing severe threats to people's physical and mental health [33]. During the initial stage of sep-

sis, the body mounts a pro-inflammatory response against pathogens; in later disease stages, pro-inflammatory responses coexist with compensatory anti-inflammatory responses. When anti-inflammatory and pro-inflammatory responses remain balanced, the body maintains homeostasis without incurring organ dysfunction. Imbalance between pro-inflammatory and anti-inflammatory responses will inevitably lead to organ dysfunction, culminating in multiple organ dysfunction syndrome. The pathophysiological process of sepsis involves multilevel damage across cellular, tissue, and organ systems. Sepsis is now recognized as a complex syndrome characterized by impaired homeostasis, encompassing immune dysregulation, neuroendocrine dysfunction, and failure of physiological barriers [34]. Advances in modern critical care medicine have deepened the clinical understanding of sepsis, leading to significant progress in diagnostic experience and therapeutic techniques, consequently resulting in a marked reduction in sepsis mortality rates. Nevertheless, some patients experience progressive clinical deterioration and poor prognosis due to prolonged ICU stays, complex underlying comorbidities, and associated pathophysiological factors such as immune system dysregulation. Concurrently, clinical studies indicate that ICU patients with sepsis frequently develop stress-induced hyperglycemia, which elevates mortality rates [35]. During sepsis onset, various inflammatory mediators directly stimulate and promote the secretion of adrenal corticosteroids, leading to abnormal expression of these hormones. Consequently, the body manifests elevated blood glucose levels. Inflammatory factors within the bloodstream further interfere with peripheral tissue glucose uptake by reducing insulin-dependent glucose uptake, inhibiting lipogenesis, and stimulating lipolysis to elevate plasma free fatty acid levels—collectively inducing insulin resistance. Blood glucose levels not only reflect the body's energy metabolism status but are also closely associated with impaired immune function. Higher blood glucose levels correlate with increased oxidative stress in myocardial mitochondria of sepsis patients, exacerbating mitochondrial damage and ultimately elevating mortality risk. Glycemic variability manifests systemic inflammatory responses and represents a complication in critical or moribund conditions. Its significant cytotoxic effects adversely impact the prognosis of adult sepsis patients in ICU settings [36]. Significant fluctuations in blood glucose disrupt internal homeostasis, playing a substantial role in the onset and progression of the disease. This occurs primarily because glycemic variability intensifies oxidative stress responses, impairs endothelial cell function, ultimately triggers neural damage, and elevates patients' mortality risk. Recent research indicates that septicemia patients, affected by infection and trauma, exhibit significant activation of the neuroendocrine system accompanied by excessive release of inflammatory mediators. At this stage, patients often develop metabolic dysregulation characterized by hypercatabolism and insulin resistance, thereby leading to elevated blood glucose levels. [37], and Kelly A C *et al.* [38] found that as blood glucose levels increase in septicemia patients, coagulation disorders are further exacerbated, wound healing and neutrophil function are adversely affected, and

susceptibility to aggravated infections leads to diminished quality of life. These findings suggest that blood glucose levels may influence the prognosis of septicemia patients. Therefore, utilizing blood glucose monitoring to predict patient outcomes has become a clinically urgent issue. Consequently, enhanced monitoring of blood glucose and glycemic variability in adult sepsis patients in the ICU is of paramount importance for disease assessment and prognosis improvement.

4. Conclusion

Abnormal fluctuations in blood glucose represent a significant clinical issue in critical care and emergency resuscitation [39]. The role of glucose variability (GV) in predicting prognosis and guiding treatment for critically ill patients is gaining increasing clinical attention, with sepsis being one such condition. Pro-inflammatory cytokines and insulin resistance form a mutually causative relationship, serving as the initiating factor triggering abnormal blood glucose fluctuations. Developing treatment strategies that maintain blood glucose within safe ranges while reducing GV is currently a key clinical focus. Future research directions should include: determining optimal glycemic variability (GV) targets for sepsis patients; developing targeted interventions for GV modulation; exploring interactions among GV, microbiome, and immunometabolism; and evaluating the impact of different glucose-lowering medications (e.g., SGLT-2 inhibitors, GLP-1 receptor agonists) on GV. Through multidisciplinary collaboration, more comprehensive sepsis blood glucose management strategies are expected to be established. Key future research priorities include: in-depth investigation into the molecular mechanisms of organ dysfunction caused by GV in critically ill patients; exploration of GV epidemiology across diverse populations and disease spectra; conducting large-scale clinical studies on GV modulation strategies; and advancing development and clinical application of novel GV-targeting therapeutics. In conclusion, glycemic variability represents a new dimension in blood glucose management for sepsis patients. Through multidisciplinary collaboration, deepening our understanding of the pathophysiological significance of GV and developing more precise monitoring and intervention methods are expected to further improve the prognosis of sepsis patients. This requires concerted efforts from basic scientists, clinicians, engineers, and patients to advance progress in the field of sepsis treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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