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**Challenges in hyperglycemia management in critically ill patients with COVID-19.**

Hyperglycemia in COVID-19

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## **Abstract**

Hyperglycemia is commonly associated with adverse outcomes especially in patients requiring intensive care unit stay. Data from the Corona Virus Disease 2019 (COVID-19) pandemic indicates that individuals with diabetes appear to be at similar risk for COVID-19 infection to those without diabetes but are more likely to experience increased morbidity and mortality. The proposed hypothesis for hyperglycemia in COVID-19 include insulin resistance, critical illness hyperglycemia (stress- induced hyperglycemia) secondary to high levels of hormones like cortisol and catecholamines that counteract insulin action, acute cytokine storm and pancreatic cell dysfunction. Diabetic patients are more likely to have severe hyperglycemic complications including diabetic ketoacidosis and hyperosmolar hyperglycemic state. Management of hyperglycemia in COVID-19 is often complicated by use of steroids, prolonged total parenteral or enteral nutrition, frequent acute hyperglycemic events, and restrictions with fluid management due to acute respiratory distress syndrome. While managing hyperglycemia special attention should be paid to mode of insulin delivery, frequency of glucose monitoring based on patient and caregiver safety thereby minimizing exposure and conserving personal protective equipment. In this article we describe the pathophysiology of hyperglycemia, challenges encountered in managing hyperglycemia, and review some potential solutions to address them.

**Key Words:** Hyperglycemia; COVID-19; Critical care; Diabetes; Diabetic ketoacidosis

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**Core Tip:** Hyperglycemia is commonly associated with adverse outcomes especially in patients requiring intensive care unit stay. Data from the COVID-19 pandemic indicates that individuals with diabetes appear to be at similar risk for COVID-19 infection to those without diabetes but are more likely to experience increased morbidity and mortality.

The proposed hypothesis for hyperglycemia in COVID-19 include insulin resistance, critical illness hyperglycemia (or stress- induced hyperglycemia) secondary to high levels of hormones like cortisol and catecholamines that counteract insulin action, acute cytokine storm and pancreatic cell dysfunction. Diabetic patients are more likely to have severe hyperglycemic complications including diabetic ketoacidosis and hyperosmolar hyperglycemic state. Management of hyperglycemia in COVID-19 is often complicated by use of steroids, prolonged total parenteral or enteral nutrition, frequent acute hyperglycemic events, and restrictions with fluid management due to acute respiratory distress syndrome. While managing hyperglycemia special attention should be paid to mode of insulin delivery, frequency of glucose monitoring based on patient and caregiver safety thereby minimizing exposure and conserving personal protective equipment. In this article we describe the pathophysiology of hyperglycemia, challenges encountered in managing hyperglycemia, and review some potential solutions to address them.

## **INTRODUCTION**

COVID-19 hospitalization rates have varied across different hospitals across the USA and can be as high as 15% among infected patients [1]. One in four patients admitted to the hospital with COVID-19 infection requires intensive care unit (ICU) level of care. Mortality rates vary widely among these patients, sometimes approaching as high as 62% [2]. Intensive care hospitalization rates of COVID-19 patients differ widely across the countries and in the United States range between 5 and 12% of the total positive cases [3]. The median duration of hospital stays among the COVID-19 patients ranges from 16 to 23 days, the median length of ICU stay is 7 to 17 days, and the average time of mechanical ventilation is about 1-12 days [4].

Both Type 1 and type 2 diabetes are frequently identified medical comorbidities in patients with severe COVID-19 infection with poor clinical outcomes. [5,6]. Diabetic patients treated with insulin prior to hospitalization also had poor outcomes [7]. Hyperglycemia (fasting blood glucose more than 125 mg/dL) is identified as an independent predictor of increased mortality in hospitalized patients without prior

diagnosis of diabetes [8]. It can be concluded from review of currently available literature that new onset hyperglycemia in non-diabetic patients and new onset diabetes in COVID-19 have poor clinical outcomes compared to people with preexisting diabetes and people with euglycemia [9]. A recent systemic review and meta-analysis reported high prevalence of diabetic ketoacidosis (DKA 63.4%), EDKA (euglycemic diabetic ketoacidosis 8.5%), hyperosmolar hyperglycemic state (HHS 1.4%) and combined DKA/HHS (26.8%) among acute diabetes-associated metabolic emergencies in COVID-19 patients. The mortality rate related to diabetes-associated acute metabolic emergencies in COVID-19 patients' range between 7.7% to 32.4%. The major factors associated with worse outcomes in these patients were the need of mechanical ventilation, acute renal failure and dual presence of hyperosmolar state and ketoacidosis [10]. Strict blood glucose control has been shown to have a protective effect with better outcomes in patients with COVID - 19 with hyperglycemia. Sardu et al reported that use of intravenous insulin infusion to achieve a substantial drop in blood glucose levels was associated with better clinical outcomes in patients hospitalized with COVID-19 [11].

## **MECHANISM OF HYPERGLYCEMIA IN PATIENTS WITH COVID-19 INFECTION**

### ***Infection mediated factors leading to hyperglycemia***

**Role of inflammatory storm:** Critical illness associated stress results in stimulation of the hypothalamic-pituitary-adrenal axis (HPA) axis. Excess release of various stress hormones (cortisol, growth hormone, catecholamines and glucagon) that follows, causes insulin resistance by decreasing the uptake of glucose in skeletal muscle and induce gluconeogenesis and glycogenolysis in liver contributing to hyperglycemia.

Inflammatory Storm associated with hyperglycemia is frequently among COVID-19 patients with preexisting diabetes, prediabetes, and/or obesity. The association between chronic inflammation and hyperglycemia and its effect on complications has been well described in literature [12-14]. This preexisting inflammatory state can further fuel added cytokine release related complications including increasing insulin resistance, acute (stress) hyperglycemia, and can lead to additional complications in patients with

diabetes. [15-18]. Severe hyperglycemia was frequently associated with elevations of inflammatory biomarkers like high sensitivity C- reactive protein (hsCRP), procalcitonin, interleukin-6 (IL-6), and D-dimers that act as important predictors for a more severe form of disease [19,20].

In the CORONADO study [21], about 11% of the participants had diabetes-related complications at admission in the form of hyperglycemia, and/or ketoacidosis. Ketosis can be explained because of discontinuation of glucose-lowering medications because of anorexia before hospital admission, a direct effect of COVID-19 cannot be ruled out. The virus binds to acetyl choline esterase-2 (ACE2) receptors which are expressed in pancreatic tissue and  $\beta$ -cells [22]. This can lead to dramatic loss of insulin secretion from pancreas which in combination with stress induced cytokine storm could lead to a rapid metabolic deterioration causing DKA or HHS.

**Role of pancreatic damage:** COVID-19 virus infects and replicates in cells of the human endocrine and exocrine pancreas resulting in morphological, transcriptional, and functional changes, leading to reduced numbers of insulin-secretory granules in  $\beta$ -cells and impaired glucose-stimulated insulin secretion leading to de novo development of diabetes [23]. Several case reports of new-onset diabetes have been reported in COVID-19 patients admitted to hospital [24]. In a population of 453 patients with COVID-19, 94 were identified with new-onset diabetes and these individuals had the greater risk of all-cause mortality compared with patients with known diabetes, hyperglycemia, and normal glucose.

#### *Treatment related factors leading to hyperglycemia*

**Role of steroids:** RECOVERY trial reported that dexamethasone significantly reduced the mortality risk by 17% in hospitalized patients with COVID-19, by 18% in the subsets of patients who required noninvasive oxygen therapy, and by 36% in the subsets of patients who required invasive mechanical ventilation making it standard of treatment in these subsets of patients [25].

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The metabolic effects of glucocorticoids on glucose metabolism are seen at numerous stages in the insulin-signaling cascade. Glucocorticoids reduce peripheral glucose uptake at the level of the muscle and adipose tissue [26]. Skeletal muscle is primarily responsible for the insulin-mediated capture of postprandial glucose and corticosteroids can induce insulin resistance by interfering directly with various components of the insulin signaling cascade [26,27]. Corticosteroids increase endogenous glucose production by glycogenolysis and gluconeogenesis [28]. Glucocorticoids also inhibit the production and secretion of insulin from pancreatic  $\beta$ -cells [29,30,31]. In adipose tissue, steroids are responsible for increased lipolysis and subsequent accumulation of non-esterified fatty acids (NEFA), which interfere with insulin-induced glucose uptake. The liver plays a major role in the control of glucose metabolism, maintaining fasting euglycemia. The abilities of glucocorticoids to induce hyperglycemia depend on their dose and the duration of exposure [32].

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Glycemic variability is highly debated for its potential role in the development of diabetic complications, glucocorticoid therapy represents a powerful trigger for glycemic excursions. Hydrocortisone boluses administered in critically ill patients were associated with a higher glycemic and insulin rate variability across all Acute Physiology and Chronic Health Evaluation (APACHE) II score grades, irrespective of potential confounders, such as type of admission, body mass index, and age as well as a previous diagnosis of diabetes [33].

**Role of nutrition:** Enteric and parenteral nutrition are frequently used in critically ill patients add rapid or persistent glucose load leading to hyperglycemia [34-37].

**Role of other therapies:** Other therapies administered often in ICU patients such as catecholamines, vasopressors, glucocorticoids and mineralocorticoids contribute to hyperglycemia mainly by augmenting insulin resistance at peripheral tissues. Immunomodulatory medications were shown to have mixed effects on glycemic control [38-42].

### Challenges in glycemic control

Optimal glycemic control in ICU is important for improved patient outcomes [43]. Patients with COVID-19 and hyperglycemia are at higher risk of worse outcomes compared with those with normoglycemia [44]. Acute hyperglycemia is associated with increased production of inflammatory cytokines and oxidative stress [45] frequently called “Inflammatory storm”.

Hypoglycemia can produce the same effects as acute hyperglycemia and independently affects mortality [46,47]. Sudden hyperglycemia as result of correcting hypoglycemia also leads to an enhancement of inflammation. Treatment of hypoglycemia should be slow and acute iatrogenic hyperglycemia should be avoided by rightful choice of dextrose delivery [48].

There is enough literature available to indicate that glucose variability can contribute to worse of the prognosis in ICU [47,49,50,51] even when glucose is kept in normal range [51]. Frequent fluctuations in blood glucose are a known risk factor for oxidative stress and the release of inflammatory cytokines. So, it seems advisable that glucose variability should be avoided [52]. Hyperglycemia interferes with the efficacy of other COVID-19 treatments. Glucocorticoid treatment has been associated with improved clinical outcomes in patients with COVID-19 but can induce and/or worsen hyperglycemia. In this case keeping normoglycemia may be challenging [53]. There is enough evidence that Tocilizumab (TCZ) in hyperglycemic patients failed to attenuate risk of severe outcomes of COVID-19 infection in both diabetic and non-diabetic patients [54].

Patients who are on existing hypoglycemia therapies before hospitalization adds to complexity of glucose management as well. Controlled diabetes before hospitalization as evidenced by low Hemoglobin A1c is favorable in predicting the insulin dosing, avoiding hyperglycemic excursions. Duration of therapeutic effects are shorter with agents like dipeptidyl-peptidase 4 inhibitors (DPP-4i), sodium-glucose-transporter-2 inhibitors (SGLT-2i), pioglitazone, alpha-glucosidase inhibitors, metformin, and short-acting Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) (exenatide and lixisenatide). The

duration of effects is longer with agents like long-acting insulins <sup>1</sup> long-acting insulins, GLP-1RA (dulaglutide, exenatide LA, liraglutide and semaglutide) [55]. Their action will add to that of insulin used during the treatment in ICU and must be considered in choosing the insulin dose.

<sup>10</sup> Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to significantly reduce cardiovascular mortality and heart failure (HF) hospitalizations in patients with Type 2 diabetes mellitus (T2DM). Given these cardiac benefits <sup>10</sup> and the low incidence of adverse events, SGLT2 inhibitors are strongly recommended as a treatment for HF, to slowdown the progression of chronic kidney disease (CKD), to decrease atherosclerosis related cardiac events in patients with T2DM <sup>21</sup> [55,56,57]. Therefore, it has become a class <sup>15</sup> of drugs widely used in clinical practice. In 2015, the Food and Drug Administration (FDA) warned that treatment with SGLT-2 inhibitors may increase the risk of Euglycemic Diabetic Ketoacidosis (EDKA) [58]. Since then, several scientific papers were published reporting the association between these drugs and EDKA [59-61]. One third of COVID-19 patients reported gastrointestinal symptoms such as diarrhea, loss of appetite, nausea, and vomiting resulting in volume depletion. Persistent glycosuria in a subset of diabetic patients using SGLT2 inhibitors results in worsening of volume depletion. Insulin resistance in COVID-19 patients causes lipolysis leading to ketosis and theoretically can precipitate ketoacidosis [62]. The risk of mortality was four-fold higher in patients with T2D compared to nondiabetic cohorts. Patients receiving incretin-based therapies (GLP - 1 receptor agonist and DDP - 4 inhibitor) had decreased risk of hospitalization, mortality and respiratory complications compared to those patients not on these medications. A relative decrease in mortality was noted in patients when DDP-4 inhibitors are continued upon admission compared with patients where these were discontinued on admission [63].

Adequate hydration of the diabetic patient with COVID-19 is essential. Hyperhydration can induce ARDS further worsening lung damage. Attention should also be paid to serum Potassium (K<sup>+</sup>) levels as patients can be at major risk of hypokalemia, likely due to hyperaldosteronism associated with COVID-19 infection. Insulin treatment may

worsen hypokalemia if not corrected in time. Spironolactone through its dual action as a mineralocorticoid receptor antagonist and an androgenic inhibitor, can help reducing risk of pulmonary edema and ARDS in COVID-19. Its potassium-sparing action by antagonizing mineralocorticoid receptors helps in minimizing the risk of hypokalemia during insulin treatment [64].

## **TREATMENT OF HYPERGLYCEMIA**

### ***Glycemic targets***

There is a paucity of literature on glycemic control among COVID-19 patients hospitalized with hyperglycemia with or without diabetes. The limited literature suggests inadequate glycemia management due to lack of established guidelines regarding the most appropriate management of hyperglycemia in patients infected by COVID-19. Meanwhile, established guidelines in non-COVID patients can be adopted with slight modifications to manage hyperglycemia in critical and noncritical care settings to care of COVID-19 patients during this pandemic. Blood sugar goals in ICU have been an active area of research and debate. Intensive glycemic control (80–110 mg/dL) compared to moderate control (140–180 mg/dL) does not provide significant benefit and can be associated with increased harm [65,66]. In many studies glucose levels above 180 mg/dL were associated with increased risk of hospital complications. However, the lower limit for glycemia target is less well established and values greater than 110 mg/dL are generally recommended to minimize the risks of hypoglycemia [67]. Clinical guidelines recommend maintaining glucose levels between 140 and 180 mg/dL for most critically ill patients [68] and more stringent goals of 110–140 mg/dL may be reasonable for selected patients if they can be achieved without significant hypoglycemia [67,68,69]. However, blood glucose levels less than 200 mg/dL were also targeted in some patients with very labile and critical forms of disease, particularly since most were also on continuous enteral or parenteral nutrition and thus in a constant postprandial state [70].

### ***Insulin Therapy***

Insulin is still the best glucose-lowering medication and recommended treatment for critically ill patients with COVID-19. The primary goals of a safe and effective insulin regimen include reducing contact frequency of health care workers with patient, reducing glucose variability, minimize risk of hypoglycemia, and optimal glycemic control [71]. There is no ideal protocol for the management of hyperglycemia in the critically ill patient and there is no clear evidence demonstrating the benefit of one protocol/algorithm versus any other. The implementation of any of these algorithms is prone to human errors and their success is greatly dependent on nursing education, clarity, and ease of understanding of instructions. To avoid errors in dosing, some institutions have adopted validated computerized protocols aiming to direct the nursing staff to adjust the insulin infusion rate [72,73]. Most important elements that increase success of any protocol using continuous insulin infusion are the rate adjustment that considers the current and previous glucose value and the current rate of insulin infusion; rate adjustment that considers the rate of change from the previous reading, and frequency of glucose monitoring.

Hemodynamically unstable patients on vasopressors; those receiving parenteral nutrition, enteral nutrition with frequent rate adjustments; those on high-dose steroids; those in diabetic ketoacidosis or hyperosmolar hyperglycemic state will need intravenous insulin infusion and will need hourly blood glucose monitoring. For hemodynamically stable patients who are not meeting the above criteria; patients with stable insulin requirements (including those on enteral feeding); subcutaneous basal insulin regimens (standard basal-bolus, basal-bolus-correction, or basal-correction) can be used. The blood sugar testing can be every 4-6 h in this cohort of patients.

Once the patient is clinically stable, intravenous insulin can be transitioned to subcutaneous administration. Initial dose of subcutaneous insulin is usually 60-80% of intravenous insulin needed in previous 24 hours. Overlap between intravenous and subcutaneous insulin is advised usually for 2-3 hours to reduce risk of rebound hyperglycemia. [74,75].

The degree of hyperglycemia and insulin resistance were associated with rapid elevations of inflammatory markers (high sensitivity CRP, Interleukin-6, procalcitonin, and D-dimers etc.). Some institutions developed predictive algorithms based on artificial intelligence to predict the glucose values corresponding to changes in inflammatory marker levels. This allows timely dosing of insulin to prevent extreme blood glucose fluctuations. [71,76].

The literature related to treatment of corticosteroid induced hyperglycemia is limited. The hyperglycemic effect of dexamethasone lasts up to 48 hours and can be treated with addition of long-acting insulin preparations like glargine or detemir whose glucose lowering effect can last longer than 24 hours [77,78]. Similarly, hyperglycemic peak of methylprednisolone develops after 4–6 h of administration. Insulin-neutral protamine Hagedorn (NPH) can be used as correctional insulin to target peak blood glucose elevation with methylprednisolone as the timeline of peak blood glucose elevation from methylprednisolone coincide with timeline of peak action of NPH insulin [79]. Therefore, clinicians who choose systemic corticosteroid treatment for their patients with COVID-19 should anticipate the occurrence of hyperglycemia and manage it based on the glycemic profile of the systemic corticosteroid. Addition of NPH insulin in the morning in addition to the existing insulin regimen can help with better glycemic control in setting of steroid use [71].

### ***Protecting Healthcare providers***

Protecting healthcare providers is also an important part of taking care of COVID-19 patients. Caregivers must use appropriate personal protective equipment (PPE) while facing procurement challenges due to nationwide shortage of PPE. Every attempt should be made to minimize unnecessary contact with patients while not compromising on care. Bundling cares including glucose checks, therapy sessions, patient repositioning can reduce frequent healthcare personnel exposure. Intravenous drips that require frequent titration like insulin can be managed from outside the patient room through long tubing.

9 Finally, consideration should be given to changing how we measure blood glucose levels in the critically ill patient. For patients on intravenous insulin infusion, blood sugar monitoring recommended every 1-2 hours, while those on subcutaneous insulin regimen, monitoring can be spaced every 4-6 hours. Patients can also participate in point of care self-glucose checks through devices approved by FDA [80].

9 US Food and Drug Administration (FDA) approved 2 continuous glucose monitors (CGM) – the Optiscanner 5000 and the GlucoScout – for remote glucose monitoring in hospitalized patients, but they are not commonly used. On April 8, 2020, FDA has excised “enforcement discretion” and temporarily sanctioned off label use and put out guidance on the potential use of CGM (Dexcom/Abbott FreeStyle Libre) in the hospital (but not for use in critically ill) during the current pandemic. In addition, studies based on use of CGM technology in hospitalized patients prior to COVID-19 pandemic have shown that several potential circumstances (both patient and management related) in the intensive care unit (e.g., MRI, use of vasoactive agents, acidosis, anasarca, dehydration, peripheral edema, hypotension, and dialysis) require careful use of this technology as they can negatively impact the accuracy of blood glucose monitoring. Hybrid models utilizing both point of care (POC) blood sugar testing and CGM a few times a day may be indicated in these situations to ensure readings are valid. [81]. Published literature regarding the use of CGM in ICU patients with COVID-19 is limited [82].

## CONCLUSION

Hyperglycemia is common and is associated with worse outcomes in COVID-19 patients admitted to ICU. The mechanism of hyperglycemia is explained by infection and treatment related factors. Established guidelines can be used as a roadmap but need to be tailored for individual patient needs. Though 18 most current guidelines recommend targeting blood glucose levels <180 mg/dL in critically ill patients, a target glucose range of 110–180 mg/dL is acceptable when tailored to individual patient characteristics and clinical situation. Insulin is still the best glucose-lowering medication and 5 should be a treatment of choice for critically ill patients with COVID-19. Intravenous insulin infusion

and subcutaneous basal insulin regimens (standard basal-bolus, basal-bolus-correction, or basal-correction) are the preferred for glycemic control hospitalized patients in critical and noncritical settings respectively. Bundling the glucose checks together with other nursing and therapist activities will minimize patient contact of health care workers and help to conserve PPE. Published literature regarding the use of CGM in ICU patients with COVID-19 is limited.

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