Challenges in hyperglycemia management in critically ill patients with 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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Kethireddy R et al. Hyperglycemia in COVID-19

**Core Tip:** Data from the corona virus disease 2019 (COVID-19) pandemic indicates that individuals with diabetes are more likely to experience hyperglycemia related complications including diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. These patients often require hospitalization to intensive care units. In this article we intend to describe the pathophysiology of hyperglycemia in critically ill patients with COVID-19 infection, challenges encountered in managing hyperglycemia, and review some potential solutions to address them.

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**INTRODUCTION**

Corona virus disease 2019 (COVID-19) hospitalization rates have varied across different hospitals across the United States 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 d, the median length of ICU stay is 7 to 17 d, and the average time of mechanical ventilation is about 1-12 d[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 systematic 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[11] 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.

**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 hypothalamo-pituitary-adrenal (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 ACE2 receptors which are expressed in pancreatic tissue and β-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 β-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].

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 β-cells[29-31]. In adipose tissue, steroids are responsible for increased lipolysis and subsequent accumulation of non-esterified fatty acids, 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].

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 glycemie 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 other 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[47,49-51] 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-LikePeptide-1 Receptor Agonists (GLP-1RA) (exenatide and lixisenatide). The duration of effects is longer with agents like long-acting insulins 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.

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 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[55-57]. Therefore, it has become a class 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 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+) 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[67-69]. 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 vs 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 diabetogenic acidosis, 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 h. Overlap between intravenous and subcutaneous insulin is advised usually for 2-3 h 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 h and can be treated with addition of long-acting insulin preparations like glargine or detemir whose glucose lowering effect can last longer than 24 h[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.

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 h, while those on subcutaneous insulin regimen, monitoring can be spaced every 4-6 h. Patients can also participate in f self-glucose checks through devices approved by FDA[80].

US 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 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 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 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.

FOOTNOTES

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REFERENCES

1 COVID-19 statistics. COVID-19 Weekly Epidemiological Update. [cited 23 March 2021]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports [DOI: 10.46234/cdc2020.032]

2 Garg S, Kim L, Whitaker M, O’Halloran A, Cummings C, Holstein R, Prill M, Chai SJ, Kirley PD, Alden NB, Kawasaki B, Yousse-Hindes K, Niccolai L, Anderson EJ, Openo KP, Weigel A, Monroe ML, Ryan P, Henderson J, Kim S, Como-Sabetti K, Lynfield R, Sosin D, Torres S, Muse A, Bennett NM, Billing L, Sutton M, West N, Schaffner W, Talbot HK, Aquino C, George A, Budd A, Brommer L, Langley G, Hall AJ, Fey A. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-19, US States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 458-464 [PMID: 32298251 DOI: 10.15585/mmwr.mm6915e3]

3 Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020; 318: E736-E741 [PMID: 32228322 DOI: 10.1152/ajpendo.00124.2020]

4 Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006; 23: 623-628 [PMID: 16759303 DOI: 10.1111/j.1464-5491.2006.01861.x]

5 Rawshani A, Kjöhlede EA, Rawshani A, Sattar N, Eeg-Olofsson K, Adiels M, Ladvigsson J, Lindh M, Gisslén M, Hagberg E, Lappas G, Eliasson B, Rosengren A. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: A nationwide retrospective cohort study. Lancet Reg Health Eur 2021; 8: 100105 [PMID: 33969336 DOI: 10.1016/j.lanepe.2021.100105]

6 Holman N, Knighton P, Kar P, O’Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020; 8: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]

7 Nguyen NN, Ho DS, Nguyen HS, Ho DKN, Li HY, Lin CY, Chia HY, Chen YC. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: A meta-analysis. Metabolism 2021; 131: 155196 [PMID: 35367460 DOI: 10.1016/j.metabol.2022.155196]

8 Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, Xu J, Wu F, Duan L, Yin Z, Luo H, Xiong N, Xu M, Zeng T, Jin Y. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia 2020; 63: 2102-2111 [PMID: 32647915 DOI: 10.1007/s00125-020-05209-1]

9 Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract 2020; 167: 108382 [PMID: 32853686 DOI: 10.1016/j.diabres.2020.108382]

10 Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 2020; 8: 782-792 [PMID: 32687793 DOI: 10.1016/S2213-8587(20)30180-7]

Kethireddy R et al. Hyperglycemia in COVID-19
Sardu C, D’Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Paolisso G, Marfella R. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? *Diabetes Care* 2020; 43: 1408-1415 [PMID: 3240456 DOI: 10.2337/dci-07-0237]

Donath MY, Shoehorn SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011; 11: 98-107 [PMID: 21233852 DOI: 10.1038/nri2925]

Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliariello E, Ciriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 2002; 106: 2067-2072 [PMID: 12375975 DOI: 10.1161/01.cir.0000034509.14906.ac]

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]

Oswald GA, Smith CC, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycemia in non-diabetic patients with myocardial infarction. *Br Med J (Clin Res Ed)* 1986; 293: 917-922 [PMID: 3094714 DOI: 10.1136/bmj.293.6552.917]

Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87: 978-982 [PMID: 11889147 DOI: 10.1210/jcem.87.3.8341]

Hill MA, Mantzoros C, Sowers JR. Commentary: COVID-19 in patients with diabetes. *Metabolism* 2020; 107: 154217 [PMID: 32220611 DOI: 10.1016/j.metabol.2020.154217]

Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Li Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Diabetes Metab J* 2021; 45: 15141377 DOI: 10.4093/dmj.2020.04.021]

Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; 373: 1798-1807 [PMID: 19465235 DOI: 10.1016/S0140-6736(09)60553-5]

Kim NY, Ha E, Moon JS, Lee YH, Choi EY. Acute Hyperglycemic Crises with Coronavirus Disease-19: Case Reports. *Diabetes Metab J* 2020; 44: 349-353 [PMID: 32347027 DOI: 10.4093/dmj.2020.0099]

Curcio B, Hadjadji S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnaudt G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittoni M, Bourron O, Bouttillon D, Caenavene-Roblot F, Chaumeil C, Cosson E, Coudal S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Lavioille B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébault JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020; 63: 1500-1515 [PMID: 32472191 DOI: 10.1007/s00125-020-05180-x]

Hamming I, Timens W, Bultghus ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203: 633-637 [PMID: 15141377 DOI: 10.1002/path.1570]

Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, Weil T, Koepke L, Bozzo CP, Read C, Fois G, Eiseler T, Gehrmann J, van Vuuren J, Wessbecher IM, Frick M, Costa IG, Breunig M, Grünert B, Peters L, Schuster M, Liebau S, Seufferlein T, Stenger S, Stienlinger A, MacDonald PE, Kirchhoff F, Sparer RKMJ, Walther P, Rickert H, Barth TFE, Wagner M, Münch J, Heiler S, Kieger A. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab* 2021; 3: 149-165 [PMID: 33536639 DOI: 10.1038/s42255-021-00347-1]

Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, Qiu K, Zhang J, Zeng T, Chen L, Zhang J. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab* 2020; 22: 1897-1906 [PMID: 32469464 DOI: 10.1111/dom.14099]

RECOVERY Collaborative Group. Horby P, Lim WS, Emberson JR, Mathur M, Bell JL, Linsell L, Stalpin N, Brightling C, Ustianowski A, Elmalı E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; 384: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2012436]

Mills E, Devendra S. Steroid-induced hyperglycaemia in primary care. *London J Prim Care (Abingdon)* 2015; 7: 103-106 [PMID: 26558039 DOI: 10.1080/17571472.2015.1082344]

van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009; 39: 81-93 [PMID: 19200161 DOI: 10.1111/j.1365-2362.2008.02067.x]

Weinstein SP, Wilson CM, Pritsker A, Cushman SW. Dexamethasone inhibits insulin-stimulated recruitment of GLUT4 to the cell surface in rat skeletal muscle. *Metabolism* 1998; 47: 3-6 [PMID: 9404690 DOI: 10.1016/S0026-0495(98)00184-c]

Vegiopoulos A, Herzog S. Glucocorticoids, metabolism and metabolic diseases. *Mol Cell Endocrinol* 2007; 275: 43-61 [PMID: 17624658 DOI: 10.1016/j.mce.2007.05.015]

Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Investig* 2002; 32 Suppl 3: 14-23 [PMID: 12028371 DOI: 10.1046/j.1365-2362.32.s3.x.x]

Deluayn F, Khan A, Cintra A, Davani B, Ling ZC, Andersson A, Ostenson CG, Gustafsson J, Efendic S, Okret S. Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids. *J Clin Invest* 1997; 100: 2094-2098 [PMID: 9329975 DOI: 10.1172/JCI119743]

van Raalte DH, Nofraste V, Bunck MC, van Iersel T, Elssaisa Schaan J, Näsander UK, Heine RJ, Mari A, Dokter WH, Diamant M. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. *Eur J Endocrinol* 2010; 162: 729-735 [PMID: 20124412 DOI: 10.1530/EJE-09-1054]

Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function
34 Lin LY, Lin HC, Lee PC, Ma WY, Lin HD. Hyperglycemia correlates with outcomes in patients receiving total parenteral nutrition. Am J Med Sci 2007; 333: 261-265 [PMID: 17505165 DOI: 10.1097/MAJ.0b013e3180536b26]

35 Bjerké HS, Shabot MM. Glucose intolerance in critically ill surgical patients: relationship to total parenteral nutrition and severity of illness. Am Surg 1992; 58: 728-731 [PMID: 1456586]

36 Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009; 361: 1088-1097 [PMID: 19741230 DOI: 10.1056/NEJMct0806956]

37 Laesser CI, Cumming P, Reber E, Stanga Z, Muka T, Bally L. Management of Glucose Control in Noncritically Ill, Hospitalized Patients Receiving Parenteral and/or Enteral Nutrition: A Systematic Review. J Clin Diet 2019; 8 [PMID: 31261760 DOI: 10.1016/j.jcnd.2019.08.004]

38 Pretty C, Chase JG, Lin J, Shaw GM, Le Compte A, Razak N, Parente JD. Impact of glucocorticoids on insulin resistance in the critically ill. Comput Methods Programs Biomed 2011; 102: 172-180 [PMID: 20801543 DOI: 10.1016/j.cmpb.2010.08.004]

39 Tamez-Pérez HE, Quintanilla-Flores DL, Rodriguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. World J Diabetes 2015; 6: 1073-1081 [PMID: 26240704 DOI: 10.4239/wjdm.v6.i10.1073]

40 Bratusch-Marrain PR. Insulin-counteracting hormones: their impact on glucose metabolism. Diabetologia 1983; 24: 74-79 [PMID: 6341138 DOI: 10.1007/BF00297384]

41 Khoury N, McGill JB. Reduction in insulin sensitivity following administration of the clinically used low-dose pressor, norepinephrine. Diabetes Metab Res Rev 2011; 27: 604-608 [PMID: 21538777 DOI: 10.1002/dmrr.1212]

42 Halter JB, Beard JC, Porte D Jr. Islet function and stress hyperglycemia: plasma glucose and epinephrine interaction. Am J Physiology 1984; 247: E47-E52 [PMID: 6377920 DOI: 10.1152/ajpendo.1984.247.1.E47]

43 van Hoolendonk RT, Binnekade JM, Bos LD, Horn J, Juffermans NP, Abu-Hanna A, Schultz MJ. Associations between bolus infusion of hydrocortisone, glycemic variability and insulin infusion rate variability in critically ill patients under moderate glycemic control. Ann Intensive Care 2015; 5: 34 [PMID: 26525053 DOI: 10.1186/s41598-015-0077-5]

44 Stoutt K, Chawla S. Don't Sugar Coat It: Glycemic Control in the Intensive Care Unit. J Intensive Care Med 2019; 34: 889-896 [PMID: 30309291 DOI: 10.1177/0885066618801748]

45 Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; e3319 [DOI: 10.1002/dmrr.3319]

46 Ceriello A, Zachir SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. J Am Coll Cardiol 2009; 53: S9-13 [PMID: 19179217 DOI: 10.1016/j.jacc.2008.09.054]

47 Bellaver P, Schaeffer AF, Dullius DP, Viana MV, Leitão CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality in critically ill patients. Sci Rep 2019; 9: 18498 [PMID: 31811218 DOI: 10.1038/s41598-019-55080-3]

48 Borzi V, Frasson S, Gussoni G, Di Lillo M, Gerlioni R, Augello G, Gulli G, Ceriello A, Solerte B, Bonizzoni E, Fontanella A; Research Department of FADOI. Risk factors for hypoglycemia in patients with type 2 diabetes, hospitalized in internal medicine wards: Findings from the FADOI-DIAMOND study. Diabetes Clin Pract 2016; 11S: 24-30 [PMID: 27242119 DOI: 10.1002/diabetes.2016.01.020]

49 Ceriello A, Novials A, Ortega E, La Sala L, Pujadas G, Testa R, Bonfigli AR, Esposito K, Giugliano D. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. Diabetes 2012; 61: 2993-2997 [PMID: 22891214 DOI: 10.2337/db12-0224]

50 Kulkarni H, Bihari S, Prakash S, Huckson S, Chavan S, Mantani M, Pilcher D. Independent Association of Glucose Variability With Hospital Mortality in Adult Intensive Care Patients: Results From the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Binational Registry. Crit Care Explor 2019; 1: e0025 [PMID: 32166267 DOI: 10.1097/CCE.0000000000000025]

51 Takashashi H, Iwashashi N, Kirigaya J, Kataoka S, Minamimoto Y, Gohbara M, Abe T, Okada K, Matsuzawa Y, Konishi M, Maejima N, Ibini K, Kosuge M, Ebina T, Tamura K, Kimura K. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. Cardiovasc Diabetol 2018; 17: 116 [PMID: 30121076 DOI: 10.1186/s12933-018-0761-5]

52 Ceriello A, Monnier L, Owens D. Glycemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019; 7: 221-230 [PMID: 30115599 DOI: 10.1016/S2213-8587(18)30136-0]

53 Berton AM, Principe N, Giordano R, Ghigo E, Grotto S. Systemic steroids in patients with COVID-19: pros and cons, an endocrinological point of view. J Endocrinol Invest 2021; 44: 873-875 [PMID: 32514902 DOI: 10.1007/s40618-020-01325-2]

54 Marfella R, Paolillo P, Sardo C, Bergamaschi L, D’Angelo EC, Barbieri M, Rizzo MR, Messina V, Maggi P, Coppola N, Pizzi C, Briffa M, Viale P, Galì N, Paolillo G. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes Metab 2020; 46: 403-405 [PMID: 32447102 DOI: 10.1016/j.diabet.2020.05.005]

55 Prattichizzo F, La Sala L, Rydén L, Marx N, Ferrini M, Valensi P, Ceriello A. Glucose-lowering therapies in patients with type 2 diabetes and cardiovascular diseases. Eur J Prev Cardiol 2019; 26: 73-80 [PMID: 31769183 DOI: 10.1177/2047487319880040]

56 Scheen AJ. Challenging 2019 ESC guidelines for the management of type 2 diabetes. Diabetes Metab 2020; 46: 181-185 [PMID: 31707046 DOI: 10.1016/j.diabet.2019.10.006]

57 Srinivas N, Sarma MK, Modi S, Pispalati Y, Vaidya S, Syed Gaggar N, Sange AH, Sange I. Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors: Delving Into the Potential Benefits of Cardiorenal Protection Beyond the Treatment of Type-2 Diabetes Mellitus. Cureus 2021; 13: e16868 [PMID: 34531443 DOI: 10.7759/cureus.16868]

58 US Food and Drug Administration. Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may
result in a serious condition of too much acid in the blood [DOI: 10.1037/e378952004-001]

59 Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. Eur J Intern Med 2019; 63: 9-14 [PMID: 30910328 DOI: 10.1016/j.ejim.2019.03.014]

60 Somagutta MR, Agadi K, Hange N, Jain MS, Battl E, Emuze BO, Amos-Arowoshegbe EO, Popescu S, Hanan S, Kumar VR, P Pomineto K. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. Curr Res 2021; 13: e13665 [PMID: 33824816 DOI: 10.7759/cureus.13665]

Almeirei M, Alsadeeqi E. Euglycemic Diabetic Ketoacidosis after Discontinuing SGLT2 Inhibitor. Case Rep Endocrinol 2020; 2020: 4101975 [PMID: 35286210 DOI: 10.1155/2020/4101975]

62 Batista DV, Vieira CAFA, Costa TA, Lima EG. COVID-19-associated euglycemic diabetic ketoacidosis in a patient with type 2 diabetes on SGLT2 inhibitor: a case report. Diabetol Int 2021; 12: 313-316 [PMID: 33133998 DOI: 10.1007/s13340-020-00473-3]

63 Nyland JE, Raja-Khan NT, Bettermann K, Hauouzi PA, Leslie DL, Kraschnewski JL, Parent LI, Grigson PS. Diabetes, Drug Treatment, and Mortality in COVID-19: A Multinational Retrospective Cohort Study. Diabetes 2021; 70: 2903-2916 [PMID: 34588086 DOI: 10.2337/db21-0385]

Kofts K, Lecowitz K, Drozdżał S, Niedźwiedzka-Rystwej P, Wojdacz TK, Grywalska E, Biernawska J, Wiśniewska M, Parcewski M. COVID-19-The Potential Beneficial Therapeutic Effects of Spironolactone during SARS-CoV-2 Infection. Pharmaceuticals (Basel) 2021; 14 [PMID: 33477294 DOI: 10.3390/ph14100171]

65 Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Abodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Greco M, Laundy M, Morgan JS, Keseicoglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Mennih ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med 2020; 48: e440-e469 [PMID: 32224769 DOI: 10.1097/CCM.0000000000004363]

66 NICE-SUGAR Study Investigators. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hewitt PC, Herritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive vs conventional glucose control in critically ill patients. N Engl J Med 2009; 360: 1283-1297 [DOI: 10.1056/nejmoa0910625]

67 Van den Berge G, Wilmer A, Herrmans G, Meersseman W, Wouters PJ, Milants I, Van Wijnegaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354: 449-461 [PMID: 16425557 DOI: 10.1056/NEJMoa052521]

68 Farrokhli F, Smiley D, Umpierrez GE. Glycemic control in non-diabetic critically ill patients. Best Pract Res Clin Endocrinol Metab 2011; 25: 813-824 [PMID: 21925080 DOI: 10.1016/j.beem.2011.05.004]

69 Pérez A, Ramos A, Carreras G. Insulin Therapy in Hospitalized Patients. Am J Ther 2020; 27: e71-e78 [PMID: 31833876 DOI: 10.1097/MJT.0000000000001078]

70 Kinsley JS, Preiser JC, Hirsh IB. Safety and efficacy of personalized glycemic control in critically ill patients: A 2-year before and after interventional trial. Endocr Pract 2017; 23: 318-330 [PMID: 27967228 DOI: 10.18553/ep161532.045]

71 Gianchandani R, Esfandari NH, Ang L, Iyengar J, Knotts S, Choksi P, Pop-Busui R. Managing Hyperglycemia in the COVID-19 Inflammatory Storm. Diabetes 2020; 69: 2048-2053 [PMID: 32778570 DOI: 10.2337/db20-0022]

72 Hamdy O, Gabbay RA. Early Observation and Mitigation of Challenges in Diabetes Management of COVID-19 Patients in Critical Care Units. Diabetes Care 2020; 43: e81-e82 [PMID: 32444458 DOI: 10.2337/dc20-0944]

73 Moghissi ES, Korytkowski MT, DiNardio M, Einhorn D, Heldman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE, American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensuss statement on inpatient glycemic control. Diabetes Care 2009; 32: 1119-1131 [PMID: 19429873 DOI: 10.2337/dc09-0920]

74 Pérez Pérez A, Contrer Gutiérrez P, Aguilar Diosdado M, Bertomeu Martínez V, Galdos Anunckay P, García de Casasola G, Gomis de Bárbara R, Palma Gannia JL, Puig Domingo M, Sánchez Rodríguez A. [Hospital management of hyperglycemia]. Med Clin (Bucar) 2009; 132: 465-475 [PMID: 19289876 DOI: 10.1016/j.medclin.2009.02.001]

75 Furnary AP, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. Am J Cardiol 2006; 98: 557-564 [PMID: 16893717 DOI: 10.1016/j.amjcard.2006.02.065]

76 Ramos A, Zapata L, Vera P, Bertese AJ, Pérez A. Transition from intravenous insulin to subcutaneous long-acting insulin in critical care patients on enteral or parenteral nutrition. Endocrinol Diabetes Nutr 2017; 64: 552-556 [PMID: 29179857 DOI: 10.1016/j.endinu.2017.08.005]

77 Zhou K, Al-Jaghibeer MJ, Lansang MC. Hyperglycemia management in hospitalized patients with COVID-19. Cleve Clin J Med 2020 [DOI: 10.3994/ccjm.87.a.0012]

78 Low Wang CC, Drinazin B. Practical approach to management of inpatient hyperglycemia in select patient populations. Hosp Pract (1995) 2013; 41: 45-53 [PMID: 23680736 DOI: 10.3808/hp.2013.04.1025]

79 Owens DR, Bolli GB. Beyond the era of NPH insulin–long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. Diabetes Technol Ther 2008; 10: 333-349 [PMID: 18715209 DOI: 10.1089/diab.2008.0023]

80 Donner T, Sarkan S. Insulin - Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. [Updated 23 Feb 2019]. In: Feingold KR, Anawalt B, Boyce A, et al, editors. Endotext DOI: 10.2337/db18-1054-p]

81 Trajanoski Z, Brunner GA, Gfferer RJ, Wach P, Pieber TR. Accuracy of home blood glucose meters during hypoglycemia. Diabetes Care 1996; 19: 1412-1415 [PMID: 8941473 DOI: 10.2337/diacare.19.12.1412]

82 Xu H, Huang S, Qiu C, Liu S, Deng J, Jiao B, Tan X, Ai L, Xiao Y, Belliato M, Yan L. Monitoring and Management of Home-Quarantined Patients With COVID-19 Using a WeChat-Based Telemedicine System: Retrospective Cohort Study. J Med Internet Res 2020; 22: e19514 [PMID: 32568727 DOI: 10.2196/19514]
