REVIEW ARTICLE

Hyperglycemic Crises in Patients with COVID-19

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ABSTRACT

Background: It is unclear whether the two hyperglycemic crises, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemic state have different characteristics in patients with COVID-19. **Objective:** The objective of the study was to describe prevalence, outcomes, and management of hyperglycemic crisis, specifically in patients with COVID-19. **Methods:** English literature search of PubMed databases supplemented by manual search from 1997 up to August 28, 2020. Search terms included hyperglycemic crises, DKA, COVID-19, acute respiratory distress syndrome (ARDS), dexamethasone, mortality, and safety. Since no randomized trials are available, all pertinent observational studies, case reports, and major organization guidelines were reviewed. **Results:** DKA occurs in 0.45–3.4% of patients with COVID-19 admitted to the hospital and results in an approximately 50% mortality rate. Excessive intravenous hydration should be avoided in patients at risk or having ARDS to avoid volume overload. In patients presenting with a hyperglycemic crisis and COVID-19 requiring oxygen or on mechanical ventilation, dexamethasone may be given after resolution of hyperglycemic crisis. Insulin doses need to be increased by 50-100% to control dexamethasone-induced hyperglycemia. Selected patients with non-complicated, both DKA and COVID-19 may be safely managed by subcutaneous rapid-acting insulin in a step-down unit with blood glucose monitoring every 2 h. This strategy may spare beds in the ICU and personal protective equipment, and decrease nursing time at bedside. **Conclusions:** Hyperglycemic crises with COVID-19 are uncommon but carry a high mortality rate. Uncomplicated cases may be managed in a step-down unit. Dexamethasone can be given after resolution of a hyperglycemic crisis.

Key words: Acute respiratory distress syndrome, dexamethasone, diabetic ketoacidosis COVID-19, hyperglycemic crises, intensive care unit, mortality, safety

INTRODUCTION

Hyperglycemic crises include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). DKA is the most common hyperglycemic emergency and occurs more commonly in patients with Type 1 diabetes.[1] Approximately one-third of the cases of DKA occurs in Type 2 diabetes.[1] In nearly 50% of patients with type 2 diabetes, DKA is the initial manifestation of diabetes.[1] It is not uncommon that DKA and HHS coexist in the same patient. In a large retrospective study of 1211 patients with hyperglycemic crisis in Atlanta area, Georgia, 38% of patients had isolated DKA, 35% had isolated HHS, and 27% had combined features of DKA and HHS.[2] The purpose of this article is to review the prevalence, outcomes, and management of patients with COVID-19 complicated by hyperglycemic crisis based on available studies and authors' experience.

Prevalence of hyperglycemic crises in COVID-19

Available studies suggest that DKA is the most common of hyperglycemic crises among patients with COVID-19. The overview of these studies is presented in Table 1. In the CORONADO French study, the largest available study dedicated to patients with COVID-19 and diabetes ($n = 1317$), 19 patients (1.4%) presented with DKA.[3] In one retrospective

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Table 1: Studies that reported hyperglycemic crises in hospitalized patients with COVID-19

Authors/country	Prevalence of hyperglycemic crises	Type of crisis	Death rates
Cariou *et al*.[3]/ France	1.4% (19 of 1317 patients with diabetes)	DKA	Not reported
Goldman *et al*.[4]/UK	1.8% (4 of 218 patients)	DKA	50%
Alkundi *et al*.[5]/UK	3.4% (8 of 232 patients)	DKA	Paradoxical higher survival in DKA patients versus non-DKA patients: 87.1% versus 50.6% (P=0.046)
Li *et al*.[6]/China	0.45% (3 of 658 patients)	DKA	Not reported
Armeni *et al*.[7]/UK	Case series of 26 patients with hyperglycemic crises	42% with DKA, 7% with HHS, 50% with combined DKA and HHS	9.1% in DKA,0% with HHS, and 7.7% in combined DKA/HHS
Chan *et al*.[9]/USA	Case series of 6 men with hyperglycemic crises	Combined DKA and HHS	66%
Chamarro-Pareja *et al*.[8]/USA	Case series of 50 patients with hyperglycemic crises	DKA	50%

DKA: Diabetic ketoacidosis, HHS: Hyperglycemic hyperosmolar state

study from the UK, 4 of 218 patients (1.8%) admitted with COVID-19 presented with DKA.[4] In another UK series, 8 of 232 patients (3.4%) with COVID-19 had DKA.[5] In one retrospective study from Wuhan, China, including 658 patients with COVID-19 admitted to the hospital, only three patients (0.45%) had DKA.[6] Therefore, available data suggest that the prevalence of DKA associated with COVID-19 is not common and ranges from 0.45% to 3.4%.[3-6]

Although DKA occurs more commonly in Type 1 diabetes,[1] most (80–88%) of the episodes of hyperglycemic crises in patients with COVID-19 occurred in patients with Type 2 diabetes.[7,8] Mixed DKA and HHS features were reported in few studies. In a retrospective study from the UK, Armeni *et al*.[7] described 26 patients with hyperglycemic crisis and COVID-19; 13 patients (50%) had combined features of DKA and HHS, 11 patients (42%) had isolated DKA, and two patients (7%) had isolated HHS. Chan *et al*.[9] reported a series of 6 men (age range 19–62 years) with COVID-19 presenting with a mixed picture of DKA and HHS.

Outcomes of the patient with COVID-19 and hyperglycemic crisis

The latest available data in the USA showed that mortality in DKA patients has dropped to 0.4%.[10] Mortality in patients with COVID-19 complicated by DKA appears to be much higher, reaching 50% in most series.[8] This finding is most likely due to older age, comorbidities, and increase disease burden by COVID-19 itself. In the largest reported series of 50 patients in Bronx area (New York) admitted with DKA and COVID-19, 25 (50%) died.[8] Likewise, among the four patients described by Goldman *et al*.,[4] two patients died, and one patient remained in a critical unit at the end of 30 days follow-up. Unexpectedly, in the series reported by Alkundi *et al*.[5] in the UK, COVID-19 patients with DKA were more likely to survive (87.1%) compared with patients without DKA (50.6%) $P = 0.046$. The reasons of the latter finding are unclear but may be related to differences in patients' characteristics, co-morbidities, and severity of COVID-19.

Mortality data regarding patients with COVID-19 complicated by isolated HHS are not available. Meanwhile, in patients with diabetes but without COVID-19 patients, it was shown that mortality was higher when DKA and HHS coexist compared with each condition alone.[2] This observation is in agreement with the outcomes of the six patients with mixed DKA/HHS reported by Chan *et al*.,[9] of whom four patients expired.

Mechanisms of hyperglycemic crisis in the setting COVID-19

It is well-known that any type of infection can precipitate a hyperglycemic crisis, particularly respiratory infection such as COVID-19.[11,12] In addition, there are two potential mechanisms whereby COVID-19 may trigger a hyperglycemic crisis. First, angiotensin-converting enzyme 2 (ACE2) functions as the receptor of the virus, causing COVID-19 (the severe acute respiratory syndrome coronavirus 2, abbreviated as SARS-CoV-2) and the virus SARS-CoV-1 responsible for the SARS epidemic in 2002–2004.[13] In addition to its presence in the lungs, ACE2 is also expressed in the β cells of pancreas.[14] Thus, binding of the SARS- CoV-2 to ACE 2 may virtually cause damage of pancreatic β-cells and cause acute diabetes.[14] Second, ACE2 catalyzes the conversion of angiotensin II to angiotensin 1–7.[13] The binding of

SARS-CoV-2 to ACE2 down-regulates ACE2 and leads to increased levels of angiotensin II.[15] The latter may decrease insulin secretion and virtually contribute to the development of hyperglycemic crisis.[16]

Factors to be considered in the management of patients with COVID-19 and hyperglycemic crisis

The management of the hyperglycemic crisis has not significantly changed in the past 30 years and consists of intravenous fluids, insulin, and potassium.[11] No specific guidelines are available for the management of the hyperglycemic crisis in patients with COVID-19. However, there are some important issues specific to COVID-19 complicated by hyperglycemic crises discussed below.

PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is a common complication of COVID-19, ranging from 41% among all patients admitted to the hospital to 71% of patients admitted to the intensive care unit (ICU).[17,18] If a patient has DKA or HHS on top on ARDS due to COVID-19, it is recommended to avoid aggressive hydration and to use intravenous fluids judiciously to avoid volume overload and worsening pulmonary edema.[7,15]

PATIENTS REQUIRING OXYGEN OR MECHANICAL VENTILATION

Data from the RECOVERY trial showed that administration of dexamethasone 6 mg/d for up to 10 days decreased 28-day mortality in patients with COVID-19 requiring oxygen or invasive mechanical ventilation, but not in patients not requiring oxygen.[19] The highest magnitude of mortality reduction was observed among patients receiving invasive mechanical ventilation, adjusted rate ratio (RR) 0.64, 95% CI; 0.51–0.81 ($P < 0.001$), followed by patients receiving oxygen without mechanical ventilation, RR 0.82, 95% CI, 0.72–0.94 ($P = 0.002$).[19] In the RECOVERY trial, 24% of patients had diabetes at the study entry.[19] Unfortunately, no data were reported regarding the effect of dexamethasone on mortality among the diabetic subgroup. In the meantime, it is well established that glucocorticoids such as dexamethasone may worsen hyperglycemia and even precipitate DKA.[20] Nonetheless, given the substantial mortality benefit achieved by dexamethasone therapy, and the relatively low-dose used, it is worthwhile to offer dexamethasone to appropriate patients with COVID-19 having DKA or HHS. However, it may be wise to start dexamethasone after the resolution of a hyperglycemic crisis, which usually takes 24–48 h. The authors recommend increasing insulin doses by 50–100% within 4 h after the administration of dexamethasone to avoid rebound in hyperglycemia. Fortunately, the mortality benefit in patients with COVID-19 was evident in a relatively late stage of COVID-19. Thus, pre-specified subgroup analysis of the RECOVERY trial showed that dexamethasone was associated with a reduction in 28-day mortality among patients with symptoms for more than 7 days but not among those with more recent symptom onset.[19] Thus, this delay may allow time for a full recovery of the hyperglycemic crisis.

PATIENTS WITH EUGLYCEMIC DKA

DKA presenting with relatively low blood glucose levels (<250 mg/dl) may uncommonly occur as adverse effects of sodium-glucose co-transporters type 2 (SGLT-2) inhibitors approved for the treatment of Type 2 diabetes.[21] Few case reports described patients with COVID-19 treated with SGLT-2 inhibitors presenting with euglycemic DKA.[7,22] Clearly, SGLT2 inhibitors should be discontinued and not resumed in the future. Treatment of euglycemic DKA follows the same protocol of classic DKA. However, if the presenting plasma glucose concentrations are less than 200 mg/dl, the early addition of D5 or D10 to intravenous fluids is recommended to allow continuing insulin administration while preventing hypoglycemia.

NEED FOR SPARING ICU BEDS AND PERSONAL PROTECTIVE EQUIPMENT (PPE)

During the current pandemic crisis of COVID-19, there is a great need for every ICU bed for the management of critically ill patients requiring mechanical ventilation. Likewise, in many places worldwide, there is a shortage of PPE. Several randomized trials have shown that uncomplicated cases of DKA can be safely and effectively managed outside the ICU in the step-down unit using rapid-acting subcutaneous insulin (lispro or aspart) every 1–2 h.[23-25] Duration of time until resolution of DKA, frequency of hypoglycemia, and length of hospital stay did not differ between patients who received subcutaneous insulin compared with those who received intravenous insulin infusion.[23-26] Moreover, in one study, there was a 39% cost saving with the use of subcutaneous insulin.[25] Interestingly, with respect to the frequency of insulin injection, no differences in the above-mentioned outcomes were demonstrated when rapid-acting insulin aspart was given subcutaneously every 2 h compared to every hour or to intravenous insulin infusion.[24] Furthermore, blood glucose levels were checked every 2 h by fingerstick in the group of patients randomized to subcutaneous insulin every 2 h.[24] Implementation of the latter strategy may be useful to reduce the frequency of patient interactions and the need for PPE.[26,27] It should be emphasized, however, that only uncomplicated cases of DKA or HHS may be managed outside the ICU. The definition of uncomplicated cases is not

well-defined in the literature. In studies using subcutaneous insulin to treat DKA, the following exclusion criteria were applied: Refractory hypotension, acute myocardial ischemia, end-stage renal and liver disease, anasarca, and pregnancy.[23-25] The authors would like to add the following exclusion criteria: Altered mental status, and any organ failure due to the concomitant COVID-19, such as respiratory failure (e.g., hypoxia and severe tachypnea). In any case, clinical judgment should be assessed on an individual basis with the final decision to be taken by the treating medical team.

CONCLUSIONS AND FUTURE NEEDS

While hyperglycemic crises, mainly DKA, occur in less than 3.5% of patients with COVID-19 admitted to the hospital, they are associated with approximately 50% mortality. In general, the treatment of hyperglycemic crises in the setting of COVID-19 is similar to non-COVID-19 patients. However, less aggressive intravenous fluid is indicated in patients with ARDS to avoid volume overload. Dexamethasone may be given to patients with COVID-19 requiring oxygen or invasive mechanical ventilation after the resolution of the hyperglycemic crisis as it decreases mortality in these patients. Meanwhile, insulin doses should be increased by 50–100% within few hours after starting dexamethasone to counteract its hyperglycemic effect. Carefully selected patients with non-complicated both COVID-19 and DKA may be managed in a step-down unit with subcutaneous insulin administered every 2 h. This policy may help sparing ICU beds and PPE and reduce nursing time at bedside. Randomized studies are urgently needed to determine the optimum management of hyperglycemic crisis in association with COVID-19. Specifically, these trials should define what is the safest type and rate of infusion of intravenous fluid, ideal protocol for insulin administration, and optimum glycemic targets.

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