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Diabetic ketoacidosis precipitated by Coronavirus disease 2019 infection: Case series

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has evolved into a devastating pandemic since December 2019. Saudi Arabia's first case was reported in March 2020. Subsequently, some 220,000 cases and 2000 deaths were recorded through July 2020. COVID-19 infection aggravates glycemic control and provokes acute hyperglycemic crises, according to some reports. We made the same observations in some of our patients diagnosed with COVID-19. However, we are unaware of any reported cases of diabetic ketoacidosis (DKA) among COVID-19 patients in Saudi Arabia.
Objective: Highlighting the significance of hyperglycemia on COVID-19 patient outcomes.
Methods: Five patients with DKA were admitted and diagnosed with COVID-19 based on real-time reverse transcription-polymerase chain reaction assays. Electronic medical records were reviewed and informed consent was obtained before reporting the index cases.
Results: Five patients presenting with DKA complicating a concurrent COVID-19 infection were reported. Three were known to have preexisting diabetes and 2 had newly diagnosed diabetes based on significantly elevated glycated hemoglobin levels at admission. Four recovered and were discharged to their homes and 1 had a complicated course and died.
Conclusions: Our cases demonstrate that COVID-19 infection can trigger DKA. DKA can occur among patients who are known to have diabetes mellitus or appears as a first presentation. Clinicians should be extremely careful in checking for admission hyperglycemia and closely monitor respiratory status during fluid resuscitation of COVID–19-related DKA. (*Curr Ther Res Clin Exp.* 2020; 81:XXX–XXX)

Introduction

A novel coronavirus, later named coronavirus disease 2019 (COVID-19) by the World Health Organization, was isolated from patients presenting with pneumonia in Wuhan, China, late last year. This viral infection spread, triggering a global health crisis. Clinical presentations of COVID-19 infection may vary. The symptoms mostly manifest as fever and upper respiratory disease. However they can include gastrointestinal disease, severe pneumonia, organ failure, and death.[1]

Diabetes mellitus has been shown to be a comorbidity that is associated with severe disease, acute respiratory distress syndrome and increased mortality in COVID-19.[2–4] The coexistence of diabetes mellitus and COVID-19 is an unfortunate situation in which 1 disease can complicate the other. Decompensated diabetes, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state, are causes of morbidity and mortality among patients with diabetes, despite advances in diagnostic criteria and treatment protocols.[5]

This study describes 5 patients with COVID-19 who presented with DKA during a Saudi Arabia outbreak.

Methodology

This case series is a descriptive study that follows a group of patients who had a diagnosis of acute hyperglycemic crisis

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upon presentation and positive real-time reverse transcription-polymerase chain reaction assays (RT-PCR) for COVID-19 infection.

A literature review using the terms *diabetes mellitus*, *acute hyperglycemia*, and *diabetic ketoacidosis*, in association with the term *COVID-19 infection* was conducted using PubMed as a primary search engine. All studies covered in the literature review were published in English from 1998 to 2020.

Detailed history, laboratory investigations, clinical course, and management outcomes were obtained from the electronic medical records of index cases and reviewed by 2 physicians. Informed consent was obtained from the patient or a family member.

Cases

Case 1

Prior history

A 44-year-old woman taking oral antidiabetes agents (metformin and gliclazide) was known to have had type 2 diabetes mellitus (T2DM) for the past 9 years, along with hypertension, rheumatoid arthritis overlapping with systemic lupus erythematosus, and lupus nephritis (treated with prednisolone, etanercept, hydroxychloroquine, and methotrexate). Her home medications did not include sodium-glucose transport protein 2 (SGLT2) inhibitors or angiotensin-converting enzyme inhibitors.

History of presenting illness

Presented to the emergency department on May 14, 2020, complaining of shortness of breath, productive cough with white sputum, central chest pain, and fever documented at 39°C for 6 days. Three days after the onset of her symptoms, she visited a medical center where she was given oral antibiotics. She became afebrile for 2 days, then her fever spiked again, accompanied by epigastric pain, nausea, vomiting, and watery diarrhea. She presented to our hospital for further care. During her illness she was not able to take her oral antidiabetes medication because she was not tolerating oral medications.

Hospital course

Initial vital signs were blood pressure 135/73 mm Hg (mean arterial pressure 94 mm Hg), heart rate 121 beats/min, respiratory rate 22 breaths/min, body temperature 39.4°C, oxygen saturation 89% by pulse oximetry on room air (requiring 2 L/min via nasal cannula to keep saturation above 92%), and body mass index 32. She was diagnosed as COVID-19 positive based on RT-PCR assay.

Upon admission, the patient's plasma glucose was 8 mmol/L (144 mg/dL), which increased within a few hours to 46 mmol/L (828 mg/dL), and her glycated hemoglobin (HbA1c) was 11%. Blood chemistry revealed blood urea nitrogen 1.2 mmol/L (reference range = 2.5–6.4 mmol/L), creatinine 96 μmol/L (reference range = 53–115 μmol/L), sodium 125 mmol/L (reference range = 136–154 mmol/L), and potassium 4.1 mmol/L (reference range = 3.5–5.1 mmol/L). Urine analysis was positive for ketones. Arterial blood gas analysis (ABGA) on room air demonstrated a high anion gap metabolic acidosis, with an anion gap of 19. A chest radiograph showed airspace disease.

Based on clinical, laboratory, and radiologic findings, the patient was diagnosed with COVID-19 pneumonia and mild DKA. She was started on empiric antibiotics and symptomatic treatment for her COVID-19 infection. She was also started on a DKA protocol with intravenous fluids and insulin, plus a stress dose steroid therapy (hydrocortisone 100 mg IV every 8 hours because she was taking prednisolone at home for systemic lupus erythematosus and RA).

The patient's DKA resolved after 8 hours on the DKA protocol (average insulin rate = 9 U/h). She then was started on insulin aspart and insulin glargine. However, her respiratory symptoms were worsening with oxygen requirements increasing. She was determined to be clinically overloaded. Diuretics were initiated and antibiotics upgraded. In this deteriorating condition, the patient developed hypoxemic respiratory failure. A chest radiograph showed bilateral patchy opacities distributed throughout the lungs. The patient was moved to the intensive care unit and put on high flow nasal cannula in the awake prone position. A computed tomography pulmonary embolism protocol was performed. No major pulmonary embolism was found, but multiple bilateral scattered patchy ground glass opacity was observed throughout the lungs, with some basal consolidation. The infectious diseases team assessed the patient and started her on tocilizumab on the fifth day following admission. She received total of 2 doses.

After 9 days of intensive care unit care, the patient was moved to the ward while receiving 2 L/min nasal canula. Two days later, her oxygen saturation was 96% on room air. During her hospital stay she received hydrocortisone as stress dose for 4 days, then resumed her home dose of prednisolone. On May 29, 2020, after a hospital stay of 16 days, the patient was discharged to a quarantine facility in stable condition on insulin therapy (Table 1).

Case 2

Prior history

The patient is a 55-year-old previously medically healthy woman.

History of presenting illness

The patient presented to the emergency department on May 16, 2020 with 4 days' history of shortness of breath, cough, and confusion that worsened progressively. She was diagnosed COVID-19 positive based on RT-PCR assay. The family denied any history of fever, sore throat, or chest discomfort. She was not taking any home medications.

Hospital course

Initial vital signs were blood pressure 82/61 mm Hg, heart rate 110 beats/min, respiratory rate 28 breaths/min, body temperature 36.1°C, and oxygen saturation 100% by pulse oximetry on 5 L via face mask. Upon admission, plasma glucose was 23.3 mmol/L (491 mg/dL), and HbA1c was 14.6%. Blood chemistry revealed blood urea nitrogen 9.5 mmol/L (reference range = 2.5–6.4 mmol/L), creatinine 105 μmol/L (reference range = 53–115 μmol/L), sodium 153 mEq/L (reference range = 136–154 mmol/L), potassium 2.7 mEq/L (reference range = 3.5–5.1 mmol/L), and positive urine ketone. Arterial blood gas analysis (ABGA) on room air demonstrated a high anion gap metabolic acidosis with pH 6.93, bicarbonate 7.7 mmol/L, and anion gap 27. Severe DKA was accordingly diagnosed.

The admission chest radiograph showed no major areas of consolidation. However, empiric antibiotics and symptomatic respiratory treatment for COVID-19 infection as well as DKA protocol were initiated. No steroids were administered during the patient's stay. Her DKA resolved after 10 hours (average insulin infusion rate = 11 U/h). On the other hand, her dyspnea and radiology findings worsened. Mechanical ventilation with proning was initiated on day 2 following admission. After 5 days, the patient was extubated and moved to a ward. Subsequent COVID-19 tests were all negative. On day 10 (May 26, 2020), the patient was discharged on insulin therapy along with metformin, and instructed to followed-up with a diabetologist.

Case 3

Prior history

A 47-year-old previously medically healthy man.

Table 1
Characteristics of case patients.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age, y	44	55	47	40	70
Gender	Female	Female	Male	Male	Male
DKA severity	Mild	Severe	Moderate	Mild	Moderate
Comorbidities	T2DM, RA/SLE overlap, Hypertension	None	None	T1DM, Hypertension	T2DM, Obesity, IHD, Dyslipidemia
Home medications	Metformin, Gliclazide, Prednisolone, Etanercept, Methotrexate, Hydroxychloroquine	None	None	Insulin Lantus*, Insulin Mixtard†, enalapril	Insulin
Length of stay, d	16	11	12	21	30
In-hospital steroids	Yes	No	No	Yes	No
Mortality	No	No	No	No	Yes

DKA = diabetic ketoacidosis; IHD = Ischaemic Heart disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; T1DM = type 1 diabetes; T2DM = type 2 diabetes.

* Sanofi-Aventis, Bridgewater Township, New Jersey.

† Eli Lilly and Company, Indianapolis, Indiana.

History of presenting illness

The patient presented to the emergency department May 25, 2020, complaining of fatigue, decreased activity, and generalized body pain for 4 days. No history of rhinorrhea, sore throat, shortness of breath, cough, chest pain, fever, headache, nausea, vomiting, abdominal pain, or diarrhea.

Before the patient's presentation, he was experiencing polydipsia, polyuria, and nocturia associated with unintentional weight loss of 35 kg (body weight was 125 kg, now 90 kg) over the prior 2 months. He was not taking any home medications.

Hospital course

Initial vital signs were blood pressure 122/83 mm Hg (mean arterial pressure 96 mm Hg), heart rate 113 beats/min, respiratory rate 33 breaths/min, body temperature 36.8°C, oxygen saturation 89% by pulse oximetry on room air (requiring 2 L/min via nasal cannula for saturation >92%) and body mass index 26.8. He was diagnosed as COVID-19 positive, based on an RT-PCR assay.

Upon admission, plasma glucose was 24 mmol/L (432 mg/dL) and HbA1c was 15.1%. Blood chemistry revealed blood urea nitrogen 4.7 mmol/L (reference range = 2.5–6.4 mmol/L), creatinine 106 μmol/L (reference range = 53–115 μmol/L), sodium 134 mmol/L (reference range = 136–154 mmol/L), and potassium 4.5 mmol/L (reference range = 3.5–5.1 mmol/L). Urine analysis was positive for ketones, ABGA on room air, demonstrated high anion gap metabolic acidosis with pH 7.1, bicarbonate 11 mmol/L, and an anion gap 25. A chest radiograph revealed air space opacities within the bilateral lower lung zones.

The patient was diagnosed with COVID-19 pneumonia based on RT-PCR assay, as well as newly diagnosed diabetes with first presentation as moderate DKA. He was started on empirical antibiotics, symptomatic treatment for his pneumonia, as well as DKA protocol with intravenous fluids and insulin.

The DKA resolved after 11 hours on DKA protocol (average insulin rate 7 U/h). He was then started on insulin aspart and insulin glargine. The next day, the patient's oxygenation worsened, saturating 88% on 10 L/min simple face mask (required 15 L/min nonrebreather mask to saturate 95%), chest radiograph showed no significant interval change, the intensive care unit team was involved, and no steroids were administered during his stay.

On day 5, the patient's oxygen requirements improved, titrated down to 6 L/min via simple face mask saturating >92%. During his stay he did not receive steroids and his oxygen concentration improved to 95% on room air. He was discharged to his home June 5, 2020, in stable condition on oral antidiabetes agents and instruction follow-up with a diabetologist.

Case 4

Prior history

A 40-year-old man who was known to have hypertension and type 1 diabetes mellitus (T1DM) taking insulin Lantus (Sanofi-Aventis, Bridgewater Township, New Jersey), insulin Mixtard (Eli Lilly and Company, Indianapolis, Indiana), and enalapril. He was not taking an SGLT2 inhibitor.

History of presenting illness

The patient presented to the emergency department June 14, 2020, with a history of epigastric pain, fever, and shortness of breath for 2 days.

Hospital course

Initial vital signs were blood pressure 104/90 mm Hg, heart rate 140 beats/min, respiratory rate 34 breaths/min, body temperature 38°C, and oxygen saturation 91% by pulse oximetry on 4 L via nasal cannula. Laboratory findings showed increased plasma glucose of 16 μmol/L (288 mg/dL), and HbA1c 11.3%. Blood chemistry revealed blood urea nitrogen 10 mmol/L (reference range = 2.5–6.4 mmol/L), creatinine 88 μmol/L (reference range = 53–115 μmol/L), sodium 138 mEq/L (reference range = 136–154 mmol/L), and potassium 4.8 mEq/L (reference range = 3.5–5.1 mmol/L). Urine analysis confirmed presence of ketones and glucose. ABGA on 4 L oxygen showed pH 7.30, bicarbonate 14.1 mmol/L, and anion gap 25. His chest radiograph demonstrated bilateral prominent vascular markings. The patient was swabbed for COVID-19 and proved positive using the RT-PCR test.

The patient was accordingly diagnosed with mild DKA and COVID-19 pneumonia. He was initiated on DKA protocol, and empirical antibiotics. His DKA resolved after 10 hours (average insulin infusion rate 5 U/h). However, his oxygen demand increased so he was started on a high flow nasal cannula and shifted to prone position. On the third day of hospitalization dexamethasone 6 mg IV daily and antiviral agents (remdesivir) were initiated. His overall status and oxygen requirements improved and he was discharged July 4, 2020. The patient followed-up with his diabetologist.

Case 5

Prior history

A 70-year-old man known to have T2DM and taking insulin, dyslipidemia and taking atorvastatin, hypertension and taking bisoprolol, obesity, and ischemic heart disease for which he was taking aspirin. At home, he was not taking angiotensin-converting enzyme inhibitors or SGLT2 inhibitors.

History of presenting illness

He was brought to the emergency department June 18, 2020, with confusion and a decreased level of consciousness for a few hours. Patient was unwell and complained of abdominal pain, decreased appetite, and generalized weakness and fatigue for few days, but had no respiratory symptoms, fever, or shortness of breath.

Hospital course

The patient's initial vital signs were normal, apart from high blood pressure (160/85 mm Hg). Admission laboratory findings showed increased plasma glucose level of 27.8 mmol/L (500 mg/dL), and HbA1c 9.9%. Urine ketones were detected. ABGA pH 7.18, bicarbonate 14 mmol/L, partial pressure of carbon dioxide 40, partial pressure of oxygen 95 with anion gap 20. His admission chest radiograph showed no major lung consolidation. He was consequently diagnosed with moderate DKA and treated with intravenous fluids, regular insulin infusion with an average rate of 6 U/h, and empiric antibiotics. DKA resolved on day 2 following admission, but his level of consciousness did not improve. He underwent a computed tomography scan of the brain that did not demonstrate any acute insult. Two days after admission his fever spiked to 38.9°C and he developed a productive cough and shortness of breath. The COVID-19 swab taken on the day of admission proved positive with the RT-PCR test. He was not given steroids during his stay.

On day 4 following admission, the patient's oxygen demand increased and he was moved to the intensive care unit, where invasive mechanical ventilation was initiated in a prone position. He received multiple antibiotics, convalescent plasma, and inotropes. However, the patient's condition did not improve. He developed bradycardia followed by cardiac arrest. Cardiopulmonary resuscitation was performed and the patient was revived after many cycles. However, his condition continued to deteriorate with sepsis and multiorgan failure. Eventually, patient died after 30 days of hospitalization (July 17, 2020).

Discussion

We have described 5 cases of COVID-19 of patients who presented with DKA complicating a COVID-19 infection. Three were known to have preexisting diabetes and 2 with newly diagnosed diabetes based on the significantly elevated HbA1c levels during admission. Four patients recovered and were discharged home in a stable condition. One had a complicated course in which he experienced sepsis and multiorgan failure. He died after 30 days of hospitalization.

Few cases were reported identifying DKA in T2DM patients as a presentation of COVID-19.[6–8] In another study, 42 (6.4%) of 658 of hospitalized patients with confirmed COVID-19 presented with ketosis on admission. Of this group, 27 (64.3%) did not have diabetes, whereas 15 (35.7%) did. Three (20.0%) of those with diabetes and ketosis had ketoacidosis. Ketosis was found to increase the length of hospital stay and mortality.[9] Contrary to this finding, another study found that COVID-19 patients with diabetes who developed DKA were more likely to survive compared with patients without DKA.[10]

The relationship between diabetes and COVID-19 is 2-sided—1 disease can complicate the other. On 1 hand, diabetes is associated with an increased risk of severe COVID-19. The triglyceride and glucose index that is a reliable surrogate marker of insulin resistance were found to be predictive of severe COVID-19 illness and mortality.[11] On the other hand, COVID-19 may worsen glycemic control and cause acute hyperglycemia crises among hospitalized patients with preexisting diabetes or induced new-onset diabetes.[12]

The pathophysiology of COVID–19-induced DKA in patients with T2DM is not well understood. Several mechanisms have been proposed. Angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor for severe acute respiratory syndrome coronavirus. ACE2 receptors are present in many organs and tissues, including pancreatic beta cells. Acute damage of beta cells of the pancreas may ensue after the coronavirus binds to ACE2 receptors in beta cells and leads to insulin deficiency and subsequent DKA in patients with T2DM, or triggers acute onset diabetes.[13] ACE2 lowers angiotensin II levels because of its conversion to angiotensin.[6–12] Angiotensin II-specific receptors are present on exocrine, endocrine, and vascular cells of the pancreas. Therefore, downregulation of ACE2 after binding with severe acute respiratory syndrome coronavirus causes an elevation in angiotensin II level resulting in vasoconstriction and reduced blood flow to islet cells, accompanied by delayed insulin release and aggravated hyperglycemia.[14] In addition, insulin counterregulatory hormones that are secreted as a result of severe illness, or stress lead to increased hepatic and renal glucose production, impaired glucose utilization in peripheral tissues, and aggravated hyperglycemia.

Chee et al.[8] noted 2 important therapeutic implications that could complicate DKA management in patients with diabetes and concurrent COVID-19. As result of downregulation of ACE2 by severe acute respiratory syndrome coronavirus 2, which causes COVID-19, the renin-angiotensin-aldosterone system (RAAS) is activated, with increased levels of angiotensin II and aldosterone. This enhanced hypokalemia risk during DKA management with intravenous insulin infusion. Careful monitoring of potassium levels and proper supplementation is accordingly required in patients presenting with DKA and COVID-19. Secondly, RAAS activation upsurges pulmonary vascular permeability that may damage lung parenchyma, and excessive fluid resuscitation during DKA management could worsen the acute respiratory distress syndrome. Hence, careful fluid monitoring and replacement is warranted in such patients.[8]

Conclusions

We report our experience with 5 patients presenting with DKA complicating a concurrent COVID-19 infection. Four recovered and were discharged to their homes and 1 had a complicated course and died. Our cases demonstrate that COVID-19 infection can trigger DKA. DKA can present in patients who are known to have diabetes mellitus or appear as a first presentation. Clinicians should be careful not to overlook admission hyperglycemia in managing COVID–19-related hyperglycemia. In addition, we observed that patient respiratory status declined after the resolution of their DKA, supporting the previously mentioned theory that activation of RAAS system due to downregulation of ACE2 following binding with severe acute respiratory syndrome coronavirus leads to pulmonary vascular permeability and thus susceptibility to fluid overload. Therefore, we recommend careful fluid replacement and monitoring in those patients. During the COVID-19 pandemic, use of telemedicine via telephone or video consultations for patients with diabetes is essential to ensure adequate glycemic control and prevent acute complications of diabetes. To the best of our knowledge, this is the first case series reporting DKA precipitated by COVID-19 infection in Saudi Arabia. Studies to identify the rate and the mechanism of COVID–19-induced DKA in patients with diabetes are warranted.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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