First-time Diabetic Ketoacidosis in Type 2 Diabetics with COVID-19 Infection: A Novel Case Series

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Key Words: COVID-19, SARS-CoV-2, coronavirus, diabetic ketoacidosis, diabetes*

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Abstract:

Background:

SARS-CoV-2 is a novel coronavirus first diagnosed in US hospitals in January 2020. Typical presenting symptoms include fever, dry cough, dyspnea, and hypoxia. However, several other symptoms have been reported, including fatigue, weakness, diarrhea, and abdominal pain. We have identified a series of patients with diabetic ketoacidosis (DKA) likely precipitated by COVID-19.

Case Series:

We describe five patients with previously known type 2 diabetes and no history of DKA, who presented to the emergency department with new-onset DKA and COVID-19.

Why should an emergency physician be aware of this?

Diabetes mellitus is a known risk factor for poor outcomes in viral respiratory illnesses, including COVID-19. Infection may precipitate DKA in patients with type 2 diabetes. Aggressive management of these patients is recommended; however, management guidelines have not yet been put forth for this unique subset of patients.

Key Words: COVID-19, SARS-CoV-2, coronavirus, diabetic ketoacidosis, diabetes*

Introduction:

SARS-CoV-2 is a novel coronavirus first discovered in Wuhan, China, in late December 2019[1] and first identified in the United States in mid-January 2020. Presenting symptoms vary but include fever, dry cough, fatigue, myalgias, abdominal pain, and diarrhea.[1,2] Patients with advanced age and medical comorbidities are at higher risk for mortality, morbidity, and need for intensive care unit (ICU) admission.[2,3] Cardiovascular disease and diabetes are associated with particularly high risk for death among patients with COVID-19.[3]

Diabetic ketoacidosis (DKA) is a life-threatening condition seen most commonly in patients with type 1 diabetes mellitus (DM);[4] however, physiologically stressful conditions such as surgery, trauma, or infection may precipitate DKA in type 2 diabetes mellitus (DM2), with approximately 30-50% of DKA cases triggered by infection.[5] DKA confers a mortality rate of approximately 5%, but notably higher mortality rates occur in the elderly and patients with concurrent acute illnesses.[5] The overall mortality in patients with COVID-19 is likely to be approximately 1-3%. However, among patients with diabetes, mortality may be over 7%, and likely higher in the elderly diabetic population.[3,6] We are unaware of any reports of DKA among COVID-19 patients or the associated mortality risk. It is unknown whether the mortality of these two conditions is additive or even exponential. Given the high-risk nature of both DKA and COVID-19, it is paramount that DKA be quickly recognized in patients with concern for COVID-19 and conversely that COVID-19 is considered as a precipitant for DKA.

To our knowledge, there are no reported cases of new-onset DKA in patients with DM2 and COVID-19 infection. In this novel case series, we report five patients who presented to the emergency department (ED) with a spectrum of respiratory complaints and were found to be in DKA, likely precipitated by COVID-19.

This case series was granted exempt status by the local Institutional Review Board. Table 1 provides demographic and laboratory details for each patient. Figure 1 shows the chest x-ray findings of the presented cases.

Case 1

A 55-year old African-American male with DM2 was brought in from home for altered mental status and hypoxia. He reported a cough for several days prior, and on the day of presentation had become confused. His initial prehospital oxygen saturation was 35%. He was given oxygen via non-rebreather mask and brought to the ED, where he was persistently hypoxic to 66% and was subsequently intubated. Initial labs were consistent with DKA, and a chest x-ray showed bilateral pneumonia (Figure 1a). He was started on a DKA protocol with an intravenous insulin drip and crystalloid fluid. He was started on antibiotics and hydroxychloroquine for presumed.COVID-19, which was confirmed by PCR testing on hospital day 2.

Upon arrival to the ICU, the patient's anion gap had closed, and he was transitioned to subcutaneous insulin. As of the time of manuscript completion, he is on hospital day 15, still intubated in the ICU, with slowly improving ventilator parameters.

Case 2:

A 57-year-old Hispanic female with a history of DM2 on glipizide and metformin presented to the ED with three days of increasing dyspnea associated with fevers and cough. She had been evaluated in the ED 12 hours earlier with a chest radiograph, electrocardiogram, an unremarkable metabolic panel, and COVID-19 testing. She was discharged with a diagnosis of pneumonia. After discharge, her vomiting and dyspnea worsened, and she returned to the ED.

Laboratory work-up at the second visit revealed laboratory abnormalities consistent with DKA (Table 1). She was tachycardic but normotensive, with tachypnea and moderate respiratory distress. She was started on an intravenous insulin drip and IV crystalloid fluids in addition to antibiotics and

hydroxychloroquine for multifocal pneumonia. She was admitted to a medical ward, her anion gap closed, and she was transitioned to subcutaneous insulin before being discharged from the hospital. She tested positive for COVID-19 on hospital day 2. Upon follow up, she was doing well at home.

Case 3:

A 38-year-old Hispanic male with a past medical history of DM2 on insulin detemir and aspart presented to the ED for one day of vomiting associated with subjective fevers, cough, and shortness of breath. He noted his blood sugars had recently been elevated to over 300. Laboratory findings were consistent with DKA. His chest XRay showed with bilateral infiltrates.

He was started on an intravenous insulin drip and given crystalloid fluids. He was admitted to a medical ward where his anion gap resolved, and he was transitioned to a subcutaneous insulin regimen. He tested positive for COVID-19 on hospital day 2 and was discharged on hospital day 3. He has remained stable and recently was seen for follow up with improved glycemic control.

Case 4:

A 45-year-old Hispanic female with a history of DM2, non-adherent with medication, presented to the ED with concerns for COVID-19 after developing headache, myalgias, anorexia, and fever. She had previously been managed with oral antihyperglycemics but had stopped taking her medications two months prior to presentation.

The patient was ill-appearing, with tachypnea and clinical dehydration. Initial laboratory findings showed DKA. She was admitted to a medical ward and treated with intravenous insulin and crystalloid fluids. Her anion gap resolved after twelve hours, and she was transitioned to a subcutaneous insulin regimen. Her COVID-19 testing returned positive on hospital day two. She was discharged after two days and has not returned to the ED.

Case 5:

A 63-year-old African American female with a history of coronary artery disease, asthma, hypertension, and insulin-dependent DM2 presented with dyspnea and cough for one week. She was severely tachypneic on arrival with a respiratory rate of 53 breaths per minute and an oxygen saturation of 95% on 6 Liters of oxygen via nasal cannula. A chest x-ray showed bilateral pulmonary infiltrates (Figure 1e). Given the respiratory distress and bilateral pneumonia, the patient was started on antimicrobial coverage as well as hydroxychloroquine, and swabbed for COVID-19, which returned positive on hospital day 2.

Initial laboratory studies (Table 1) were consistent with DKA. She was intubated for refractory hypoxia. Despite attempts to match her intrinsically high minute ventilation, the patient's acidosis continued to worsen, resulting in near cardiac arrest several hours later with severe hemodynamic instability. She received bicarbonate with improvement of circulation and perfusion. Although the patient's anion gap closed and DKA resolved, she developed worsening multi-organ system failure despite maximal ventilatory and vasopressor support. Ultimately, the patient was made Do Not Resuscitate and was palliatively extubated on hospital day 4.

Discussion:

These five cases of new-onset DKA in Type 2 diabetics highlight a previously undescribed presentation of patients with COVID-19. While COVID-19 has not previously been reported as a precipitant of DKA, cases of fulminant DKA have been observed with other viral infections, such as influenza. For example, Moghadami et al described two patients that presented to emergency care in DKA presumed secondary to H1N1 influenza, both of whom ultimately died.[7] It is well known that DKA has a strong association with activated innate immune cells secondary to infection.[2,8] What is unusual about our cases is the severity of DKA in previously controlled diabetics. Notably, glipizide, a drug inherently dependent on endogenous pancreatic function, was used for hyperglycemic control in cases 1 and 2. While these patients may have been advancing in their disease, their rapid evolution from DM2 to DKA suggests a more acute precipitant. This rapid progression, in conjunction with the known cytokine

release of COVID-19,[9] raises the possibility that the intense cytokine release associated with COVID-19 may play a role in the insulin dysregulation seen in these patients.[10] Another possibility is that these patients were sustaining pancreatic injury to beta-islet cells, as a recent study has shown a high rate of pancreatic injury in COVID-19 infection.[11] It is important to note that in our case series, all patients had a relatively high hemoglobin A1c, ranging from 9.5 to 11.9 This may suggest that suboptimal glucose control predisposes to more severe forms of COVID-19 or to the precipitation of DKA. We also note that 3 of our 5 patients were Hispanic. Although there is no pathophysiologic basis to suspect that Hispanic patients would be at higher risk for COVID-19 associated DKA, this is notable in that our hospital population is only approximately 10% Hispanic. Further study is needed to help elucidate risk factors for the development of DKA among diabetic patients with COVID-19.

Although the definitive pathophysiology behind SARS-CoV-2 acting as a precipitant for DKA in people with DM2 is unknown, this illness pattern does have important implications. For instance, patients with DKA often rely on compensatory tachypnea for the regulation of acidosis, but this may be difficult to manage in COVID-19 patients. Due to aerosolization concerns with COVID-19 and constraints of negative pressure room supply, many centers are moving away from non-invasive positive pressure ventilation (NIPPV) and instead utilizing high flow nasal cannula (HFNC) or early intubation strategies. High flow nasal canula allows providers to either avoid intubation or to optimize preoxygenation for early intubation and mechanical ventilation.[12] This clinical predicament may have contributed to the poor outcome in Case 5 of our series, as shortly after intubation, the patient spiraled into profound metabolic acidosis, hemodynamic instability, and ultimately, multi-organ system failure. Another important implication of co-existing DKA and COVID-19 infection is how to manage fluid balance. Intravenous crystalloid is a staple in the resuscitation of patients with DKA, but its use has been drawn into question for patients with COVID-19 pneumonia for fear of worsening respiratory status and oxygenation. Further studies on the optimal management of concurrent acidosis and respiratory insufficiency from pneumonia in patients suffering DKA precipitated by COVID-19 would be of great use.

Why should an emergency physician be aware of this?

In the midst of the current pandemic, COVID-19 infection should be considered as a possible precipitant in patients with DKA. Minute ventilation matching and judicious fluid resuscitation are essential to the management of the combined DKA and COVID-19 disease processes. It is paramount to identify patients in this cohort in order to protect healthcare workers while intervening aggressively to optimize patient outcomes.

Citations:

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;

2. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020;

3. Vital Surveiilances: The Epidemiological Characteristics of Novel Coronavirus Diseases (COVID-19) [Internet]. China CDC. 2020;Available from: http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

4. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association [Internet]. In: Diabetes Care. 2006 [cited 2020 Apr 12]. p. 2739–48.Available from: http://www.ncbi.nlm.nih.gov/pubmed/17130218

5. Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: Risk factors and management strategies. Treat. Endocrinol. 2003;2(2):95–108.

6. COVID-19 National Emergency Response Center, Epidemiology and Case Management

Team KC for DC and P. Coronavirus Disease-19: The First 7,755 Cases in the Republic of Korea. Osong Public Heal Res Perspect 2020;11(2):85–90.

7. Moghadami M, Honarvar B, Sabaeian B, et al. H1N1 Influenza Infection Complicated with diabetic ketoacidosis. Arch Iran Med 2012;15(1):55–8.

8. Odegaard JI, Chawla A. Connecting type 1 and type 2 diabetes through innate immunity. Cold Spring Harb Perspect Med [Internet] 2012 [cited 2020 Apr 13];2(3):a007724. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22393536

9. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China.

10. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked? J Biomed Sci 2016;23(1).

11. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Journal Pre-proof Pancreatic injury patterns in patients with COVID-19 pneumonia. ncbi.nlm.nih.gov [Internet] 2020 [cited 2020 Apr 12];Available from: https://doi.org/10.1053/j.gastro.2020.03.055

12. Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults with COVID-19. JAMA - J. Am. Med. Assoc. 2020;E1–3.

Conflicts of Interest:

No authors have any conflicts of interest. Blinded to author names.

Figure 1: Features of chest radiograph of selected cases. (A) Case 1, bilateral interstitial opacifications with endotracheal tube in place. (B) Case 2, mild interstitial prominence of left lower lobe. (C) Case 3, clear chest. (D) Case 4, developing right upper and lower interstitial prominences. (E) Case 5, extensive severe bilateral disease with interstitial and basilar predominance.

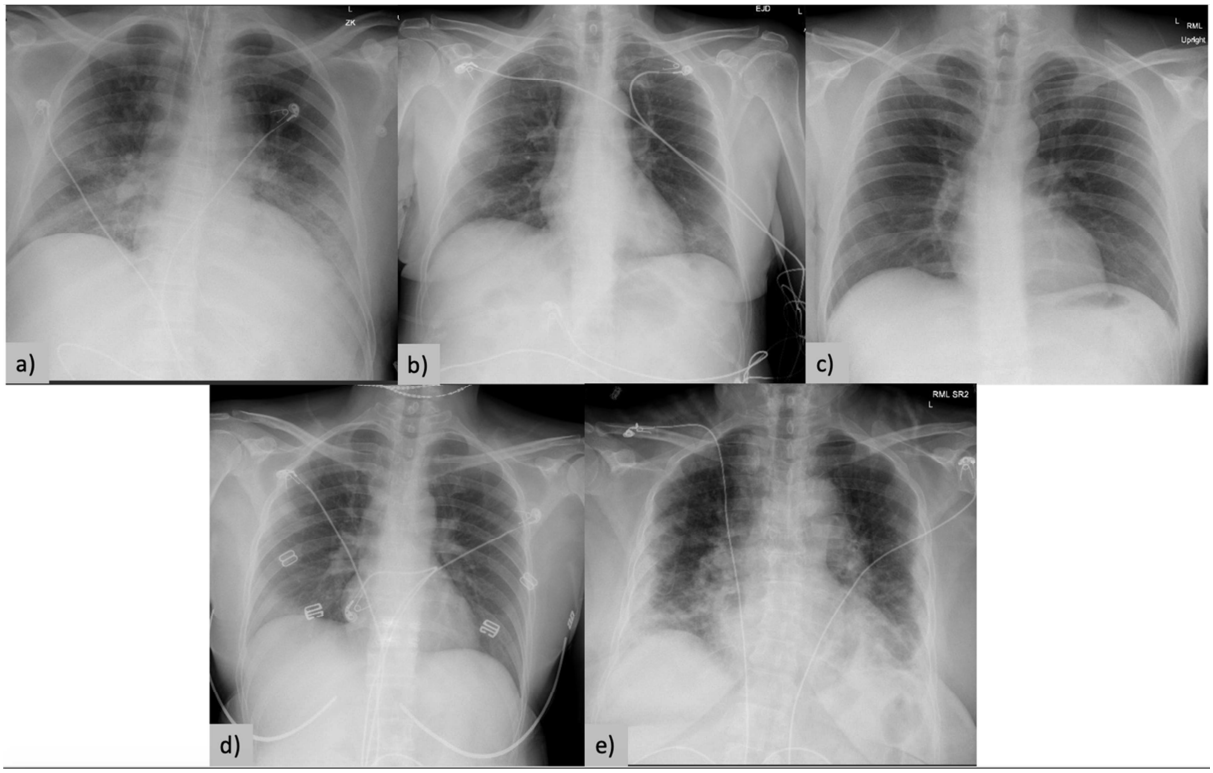
Table 1: Characteristics of Patients Presenting with Diabetic Ketoacidosis and COVID-19 Infection

Case	1	2	3	4	5	Average
Demographics						
Age	55	57	38	45	63	49
Sex	Male	Female	Male	Female	Female	
Body Mass Index	31.1	19.8	29.1	21.4	36.2	27.5
Patient Disease Characteristics						
Diabetes Medications	Glipizide	Metformin, Glipizide	Insulin detemir and aspart	None	Insulin	
Hemoglobin A1C	9.5	11.3	11.9	15	9.8	11.5
Presentation Characteristics						
Heart Rate	91	122	129	116	97	114
Blood Pressure	161/77	128/75	99/68	115/75	150/90	126/74
Respiratory Rate	55	32	20	18	53	31
SpO2	66% on NRB	97	99	100	95% on 6L	91
Glasgow Coma Score	11	15	15	15	15	14
Initial Glucose	948	227	399	342	749	533

pH	7.13	7.11	7.02	6.99	7.21	7.06
Anion Gap	21	24	22	18	18	21
Beta-hydroxy Butyrate	0.75	9.36	n/o	7.83	n/o	5.98
COVID-19 Laboratory Values						
Creatine kinase	545	n/o	n/o	n/o	329	437
C-Reactive Protein	>19.0	18.2	n/o	n/o	>19.0	18.7
D-dimer	5.44	1.06	n/o	n/o	>35.2	13.9
Ferritin	1214	337	n/o	n/o	>16,500	6,017
Fibrinogen	600	n/o	n/o	n/o	n/o	-
Lactate Dehydrogenase	931	n/o	n/o	n/o	3,934	2,433
Procalcitonin	1.38	0.16	n/o	n/o	3.65	1.73
Troponin	n/o	<0.02	n/o	n/o	2.23	1.13
Hospitalization Characteristics						
Fluid to gap closure (mL)	2125	4625	3100	5550	6160	3850
Time to gap closure (minutes)	38	900	194	720	650	463
Length of Stay (Days)		8	4	3	4	4.75
Outcome	Hospitalized at time of printing	Discharge home	Discharge home	Discharge home	Death	

n/o - not obtained

*Room air oxygen saturations (SpO2) were not available for all patients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