Case Report

COVID-19 Presenting With Diabetic Ketoacidosis: A Case Series

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A B S T R A C T

Objective: Diabetes mellitus has been recognized as one of the comorbidities that predict the severity of illness in patients infected with COVID-19. The characteristics of patients presenting with diabetic ketoacidosis (DKA) and COVID-19 infection have not been described.

Methods: We describe 5 patients with DKA and concomitant COVID-19 admitted to the intensive care unit of an academic medical center. Three patients had type 1 diabetes mellitus, and 2 patients had type 2 diabetes mellitus.

Results: While DKA with an infectious etiology is a common presentation, we observed that the patients with DKA precipitated by COVID-19 presented with atypical symptoms. COVID-19 infection was revealed during search for an etiology of DKA.

Conclusion: It is prudent to have a low threshold to screen for COVID-19 infection in patients with DKA.

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Introduction

In December 2019, a group of patients with a lower respiratory tract infection caused by a novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 were identified in China; the infection later spread across continents, resulting in a pandemic.1 The median incubation period is up to 14 days, and the most common manifestations are those causing a lower respiratory tract infection, such as fever, cough, and shortness of breath leading to an acute respiratory distress syndrome, and multiorgan failure in severe cases.1 The extent of direct organ involvement by the virus is a subject of interest, and research on various fronts is ongoing. In the past 2 decades, several viral epidemics have been reported, including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003, H1N1 influenza in 2009, and Middle East respiratory syndrome coronavirus in 2012.1 Diabetes and hyperglycemia are independent predictors of death and morbidity in patients with SARS-CoV infection.2 Animal studies in mice have shown that immune dysregulation due to long-standing diabetes leads to severe disease and prolonged lung pathology with the Middle East respiratory syndrome coronavirus infection.3 Data from Canada has shown up to 4 times higher risk of intensive care unit admission in patients with H1N1 influenza and diabetes.4

Diabetes mellitus has been recognized as one of the comorbidities that predicts the severity of illness in patients infected with COVID-19 as well.5,6 It has also been shown that patients with diabetes have higher serum levels of proinflammatory markers such as interleukin 6, C-reactive protein, ferritin, and D-dimer.5 A study of 174 patients by Guo et al7 has found that patients with diabetes are at an increased risk of severe pneumonia, uncontrolled inflammatory responses, and hypercoagulable state. Similar data have been reported from other countries, including the United States of America (USA).7

The latest data from China and New York City, USA, suggest that the prevalence of diabetes is higher in patients with severe COVID-19 infection.8,9 A nationwide analysis of 1590 patients with COVID-19 infection in China has shown that hypertension is the most prevalent comorbidity (16.9%), followed by diabetes mellitus

Abbreviations: COVID-19, coronavirus disease-2019; DKA, diabetic ketoacidosis; GI, gastrointestinal; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV2, Severe Acute Respiratory Syndrome coronavirus 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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Diabetes was highly prevalent (34.9%) in patients with severe COVID-19 infection. A prospective cohort study of 5279 patients with COVID-19 infection from New York City, USA, has shown that male patients are more likely to require hospitalization. The factors associated with critical illness included age >64 years, heart failure, body mass index >40 kg/m², male sex, and diabetes.

We report 5 consecutive patients with COVID-19 presenting with diabetic ketoacidosis (DKA) at an academic medical center. COVID-19 was diagnosed in all the patients by polymerase chain reaction using nasopharyngeal swabs. Data were collected from a review of electronic medical records. Per the institutional review board’s policy, approval was waived, given the number of patients and retrospective nature of the collection of data.

Case Report

Of the 5 patients described in detail in the Table, 3 patients had type 1 diabetes mellitus (T1DM) and 2 had type 2 diabetes mellitus (T2DM). Patient 1 in our series was 1 of the first patients with DKA and COVID-19 infection at our hospital. Her medical history was significant for T1DM (glutamic acid decarboxylase 65 antibody positivity), hypertension, hyperlipidemia, chronic kidney disease, and hypothyroidism. She presented with abdominal pain and diarrhea, likely due to concomitant Clostridium difficile colitis, which had since been diagnosed. She was incidentally noted to have COVID-19 infection when tested upon admission as a part of the workup for DKA, and she developed respiratory symptoms later during the hospitalization. She received hydroxychloroquine and supportive care for the management of respiratory failure and oral vancomycin for the C. difficile colitis. DKA improved with standard management care. Similarly, patient 2, with T1DM (had a low C-peptide level of 0.05 nmol/L at the time of the diagnosis in the setting of a significant family history of diabetes in her parents), hypertension, and hyperlipidemia, presented with nonspecific symptoms such as generalized weakness, poor appetite, and chills. She was found to have DKA on admission, and a workup for etiology revealed COVID-19 infection. Throughout her hospital course, the patient did not develop any symptoms typical of COVID-19 infection. She did not receive any COVID-19–specific therapy. Patient 3, with a medical history significant for T1DM (with a reported family history of the same), end-stage renal disease, and heart failure with a reduced ejection fraction, presented with a chief complaint of fever and was found to have DKA and COVID-19 infection. He developed hypoxic respiratory failure shortly after admission, which improved promptly with dialysis and correction of volume overload. No specific therapy for COVID-19 infection was given. The respiratory failure was likely multifactorial secondary to the COVID-19 infection and volume-overload state.

Patients 1, 2, and 3 were on subcutaneous insulin glargine once a day, with premeal humalog insulin 3 times daily at home. Patients 1 and 3 endorsed to comply with a home regimen of insulin. Patient 2 missed 2 doses of insulin deliberately to avoid hypoglycemia in the setting of poor oral intake. Autoantibodies for T1DM were not tested in patients 2 and 3.

Patients 4 (on empagliflozin) and 5 (on a combination of sitagliptin and glipizide) had T2DM and presented with symptoms suggestive of COVID-19 infection, such as fever, cough, and shortness of breath, rapidly deteriorating to acute hypoxic respiratory failure leading to mechanical ventilatory support requirement and septic shock with multiorgan involvement. Both the patients were found to have DKA on admission, for which standard management care was given. Autoantibodies for T1DM were not tested in patients 4 and 5. These patients did not have a past history of DKA despite having experienced multiple prior admissions for sepsis secondary to various other infections, such as pneumonia and infected diabetic foot ulcers. Patient 4 was enrolled into a remdesivir randomized control trial. Care for patient 5 was withdrawn by her family, who acted as a proxy as per her wishes, because of the rapid clinical deterioration.

It is interesting to note that the presentation of patient 4 was consistent with that of euglycemic DKA. This is being increasingly reported with the use of sodium-glucose transport protein 2 inhibitors or glirozins. Their mechanism of action by preventing the reabsorption of glucose and facilitating glucosuria is thought to play a role in euglycemia even in the DKA state. To date, there are a few case reports of patients presenting with COVID-19 infection and euglycemic DKA with the use of a sodium-glucose transport protein 2 inhibitor. However, there is no proposed specific pathogenesis in the setting of COVID-19 infection.

Of the 5 patients, 4 patients improved clinically and were eventually discharged. Based on the presenting clinical picture, it appears that COVID-19 infection was the precipitating cause of DKA in the patients described above.

Discussion

SARS-CoV-2 causing COVID-19 uses angiotensin-converting enzyme 2 receptors for entry into cells, a mechanism similar to that of SARS-CoV infection of 2002-2003. The angiotensin-converting enzyme 2 receptors are present on pancreatic islet cells. SARS-CoV infection has been shown to cause hyperglycemia during an acute infection, which may be due to transient damage to the pancreatic islets by the virus. Given the overlapping pathophysiology of COVID-19 infection with that of SARS-CoV, further studies are needed to explore this potential effect on β cells.

The glutamic acid decarboxylase antibodies were present in the first patient. They were not tested in the other 4 patients. These patients were clinically diagnosed with T1DM or T2DM. Two of our patients with DKA had T2DM, and this was their first episode of DKA. DKA is common in T1DM patients, and it has also been well described in patients with T2DM. Insulin resistance triggered by acute infections can precipitate relative insulin deficiency, thereby triggering diabetic ketoacidosis. Patients 4 and 5, therefore, had ketosis-prone T2DM. As mentioned above, patient 4 was also on empagliflozin, which likely contributed to the ketoacidosis.

About 50% to 75% of patients with DKA present with symptoms such as nausea, vomiting, and abdominal pain. These symptoms resolve rapidly with the correction of the underlying metabolic derangement and ketosis. The exact pathogenesis for these symptoms is unclear. It is possible that hyperglycemia, increased circulating glucagon level, and catecholamines play a role in gastric motility, contributing to these symptoms. About 10% to 12% of patients with COVID-19 infection have also reported gastrointestinal (GI) symptoms such as diarrhea (7.6%) and nausea and vomiting (4.6%). In an analysis by Parasa et al, about 30% to 50% of patients had fecal swabs that tested positive for COVID-19 infection. The GI symptoms might have been under-reported and masked by the overwhelming systemic inflammatory response and respiratory symptoms. This overlap of the GI symptoms in patients with COVID-19 infection and DKA is indeed interesting.

It is noteworthy that the patients with T1DM present with symptoms atypical of COVID-19 infection. While this might be a coincidence, it is also possible that patients with diabetes are more prone to effects on multiple organs compared to the predominant lung involvement in nondiabetic patients. Hence, it is prudent to consider having a low threshold to screen for COVID-19 infection in patients with diabetes mellitus.
| Table  Clinical Manifestations of Patients With DKA and COVID-19 Infection |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patient 1                  | Patient 2                  | Patient 3                  | Patient 4                  | Patient 5                  |
| Age (y) 67                | 61                         | 62                         | 65                         | 87                         |
| Sex Female                 | Female                     | Male                       | Male                       | Female                     |
| Race African American      | African American           | African American           | African American           | Caucasian                  |
| BMI (kg/m²) 24.96          | 31.95                      | 23.57                      | 30.34                      | 28.59                      |
| Past medical history Type 1 DM, CHF, CKD | Type 1 DM, HTN, hyperlipidemia | Type 1 DM, ESRD, CHF, PVD, HTN | Type 2 DM, PVD, COPD | Type 2 DM, atrial flutter, asthma, CAD |
| Family history Father with COPD | Parents, brothers, and sister with DM; parents with HTN and CHF | Mother with melanoma and psoriasis | Unknown | Mother with CAD; daughter with type 2 DM and CAD |
| Relevant medications prior to admission Insulin glargine, insulin lispro, lisonpril, plavix | Insulin glargine, insulin lispro, gabapentin | Insulin glargine, insulin aspart, keppra, coreg, amlodipine, aspirin, lipitor | Empaglifozin, Symbicort, albuterol, aspirin | Januvia, glipizide, pravastatin |
| Presenting complaint Fever, altered mental status, abdominal pain, and watery diarrhea | Generalized weakness, poor appetite, and chills | Fever | Fever, cough, shortness of breath leading to acute hypoxic respiratory failure, intubation, and septic shock |
| Laboratory data on admission pH 7.01 | 7.34                      | 7.33                      | 7.22                      | 7.31                      |
| Serum bicarbonate (mmol/L) <5 | 20                        | 16                        | 9                          | 17                        |
| Serum glucose (mg/dL) 821 | 587                        | 625                        | 158                        | 583                        |
| Anion gap 30 | 19 | 40 | 26 | 21 |
| β-hydroxy butyrate (mmol/L) >13.5 | 1.73 | 4.40 | 8.3 | 2.09 |
| BUN (mg/dL) 39 | 12 | 72 | 24 | 47 |
| Creatinine (mg/dL) 2.7 | 0.9 | 10.6 | 1.2 | 1.7 |
| Lactic acid (mmol/L) 2.6 | 1.8 | 1.1 | 0.7 | 1.9 |
| HbA1C (%) 8.4 | 10.8 | 10.0 | 8.9 | 7.9 |
| Severity of DKA per Kitabchi criteria Moderate | Mild | Mild | Moderate |
| Acute kidney injury Present | No acute pulmonary process | No acute pulmonary process | Minimal pulmonary vascular congestion and mild cardiomegaly | No Diffuse bilateral interstitial and air-space abnormalities | Present Bilateral scattered ground-glass opacities |
| Chest X-ray (on admission) No acute pulmonary process | No acute pulmonary process | Minimal pulmonary vascular congestion and mild cardiomegaly | No Diffuse bilateral interstitial and air-space abnormalities | Present Bilateral scattered ground-glass opacities |
| Previous history of DKA Yes | Yes | Yes | Yes | No |
| Hospital course Diagnosed with C. difficile infection and treated with oral vancomycin. Developed acute hypoxic respiratory failure likely secondary to COVID-19 infection. Received IV insulin as management for DKA and was eventually transitioned to SQ insulin at the time of discharge. | Received IV insulin as management for DKA and was eventually transitioned to SQ insulin at the time of discharge. | Received IV insulin as management for DKA and was eventually transitioned to SQ insulin at the time of discharge. | Received IV insulin as management for DKA and was eventually transitioned to SQ insulin at the time of discharge. | Developed acute hypoxic respiratory failure due to COVID-19 infection, followed by multiorgan failure. Received IV insulin for DKA until care was withdrawn. |
| Length of stay (d) 4 | 4 | 6 | 15 | 5 |
| Disposition Discharged for home | Discharged for home | Discharge to a skilled nursing facility | Discharge to a skilled nursing facility | Deceased (care withdrawn by family) |

Abbreviations: BMI – body mass index; CAD – coronary artery disease; CHF – congestive heart failure; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease, COVID-19 – coronavirus disease-2019; DKA – diabetic ketoacidosis; DM – diabetes mellitus; ESRD – end-stage renal disease; HTN – hypertension; IV – intravenous; PVD, peripheral vascular disease; SQ – subcutaneous.
Four of our 5 patients were African American. There is a growing concern for health care disparity in African American populations, contraction of virus, and severity of illness.\(^1\) When compared with counties with a majority of White population, counties with an African American majority have a 3 times higher rate of infection and 6 times higher mortality rate. This discordance may be partly explained by the higher prevalence of cardiovascular disease and other comorbidities in African American patients.\(^2\) Minorities live in densely populated neighborhoods, where social distancing is impractical.\(^3\) At this time, it is not known whether genetic host differences among races in the predisposition to contracting the virus or the severity of illness.\(^4\) A low socioeconomic status is an independent risk factor for mortality in many health scenarios. Thus, the factors underlying the predisposition of African Americans to COVID-19—related illness are multifactorial and remain incompletely understood.\(^5\)

**Conclusion**

With the worldwide number of patients with diabetes mellitus nearing 500 million, COVID-19 is likely to have a significant impact on health care. It is imperative to attain further understanding of the intricate relationship between these 2 global diseases. Viral pandemics continue to pose a significant health care burden in this rapidly growing vulnerable population with diabetes.

**Disclosure**

Dr Sandeep Dhindsa is a consultant at Bayer and Clarus Therapeutics. The other authors have no multiplicity of interest to disclose.

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