Endocrinology, Diabetes & Metabolism CASE REPORTS

A Ramos-Yataco and others | DKA and COVID-19 in patients with T2DM

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# DKA in patients with pre-existing type 2 diabetes mellitus related to COVID-19: a case series

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## Summary

The first case of the novel coronavirus infection (COVID-19) in Peru was reported on March 6, 2020. As of September 7, 2020, about 700 000 cases of COVID-19 resulting in 29,976 deaths have been confirmed by the Ministry of Health. Among COVID-19 patients with co-morbidities, type 2 diabetes mellitus (T2DM) has been recognized as a risk factor for severe disease. Patients with T2DM may experience diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic (HHS) if infected with the coronavirus 2 (SARS-CoV-2). Regular blood analysis including arterial blood gas is essential in monitoring the care of patients with T2DM infected with COVID-19. We report five cases of DKA in patients with underlying T2DM that presented with severe COVID-19 infection.

### Learning points:

- COVID-19 may cause acute metabolic dysregulations in patients with T2DM.
- It is important to monitor basic metabolic panel (BMP) and arterial blood gases (ABGs) in patients with COVID-19 since metabolic complications can develop unexpectedly.
- Patients with T2DM develop an inflammatory syndrome characterized by severe insulin resistance and B cell dysfunction that can lead to DKA.

## Background

In December 2019, the first case of COVID-19 was reported in Wuhan, China (1, 2). On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic (3). COVID-19 primarily presents with upper respiratory symptoms; the symptoms may progress to pneumonia which may lead to respiratory failure and, in severe cases, death (4). Several complications related to COVID-19 have also been reported such as thrombotic events, CNS involvement, and cardiovascular complications (5, 6). A higher mortality rate and a worse clinical course have also been reported in patients with T2DM (7, 8). In addition, recent data have emerged regarding metabolic complications especially in patients with T2DM (9, 10). According to the Johns Hopkins Coronavirus Resource Center, Peru is one of the countries with a high prevalence of COVID-19 infections worldwide (11). In Peru, 683 702 cases of COVID-19 have been diagnosed resulting in 29 687 deaths reported by the National Ministry of Health. There is no exact data about how many of the total cases had Diabetes mellitus (DM).

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However, among those who died, approximately 43.1% had DM as a comorbidity. In Nasca, 80 deaths of 4817 cases have already been reported by the National Ministry of Health (12). This study reports 5 T2DM patients with COVID-19 presenting with DKA during an outbreak in a small city in Peru.

## Case presentation and investigation

### Case 1

A 67-year-old female with a 10-year history of T2DM complicated with retinopathy, and neuropathy. Current medications are glibenclamide, metformin, and gabapentin, with an HbA1c of 5.7%. The patient was transferred to the emergency department (ED) by her primary care physician due to dyspnea. On admission, the patient's vitals were as follows: heart rate of 89 b.p.m., respiratory rate of 20 cycles per minute (cpm), and an oxygen saturation of 85% on room air. The patient was tested for COVID-19, which returned a positive result. Patient was transferred to the intensive care unit (ICU) and COVID-19 protocols were started. The patient did not need mechanical ventilation and her status gradually improved. The patient was eventually transferred out of the ICU. On the 8th hospital day, the patient was noted to be unresponsive and hypotensive. Measurements of arterial blood gases (ABGs), electrolytes, and serum ketones were immediately taken (Table 1). The patient was diagnosed with moderate DKA and she was transferred back into the ICU. Fluid resuscitation and insulin administration via drip were initiated. On the 10th hospital day, persistent hypotensive episodes were observed, hence the administration of epinephrine was initiated. On the 15th hospital day, the patient was eventually discharged and was started on a basal insulin (18 units) and rapid-acting insulin (5 units before meals). The patient was followed up for 3 weeks and she later continued with the same regimen.

### Case 2

A 45-year-old man with T2DM on Metformin with an HbA1c of 5.5%. The patient presented to the emergency room with a 1-day history of altered mental status and shortness of breath. On admission, her heart rate was 120 b.p.m., respiratory rate was 35 cpm, and oxygen saturation was 90% on room air. The levels of ABGs, electrolytes, and serum ketones were measured (Table 1). The patient was tested for COVID-19 and a positive result was obtained. The patient was transferred to the ICU with a diagnosis of severe DKA and COVID-19. Insulin drip and bicarbonate infusions were initiated, along with fluid resuscitation. The patient was also started on ceftriaxone, azithromycin, enoxaparin, and oxygen inhalation with 5 L $O_2$ via a nasal cannula as part of our protocol for COVID-19. On the 3rd hospital day, the patient's anion gap closed and DKA resolved and he transitioned from insulin drip to NPH: 24 units subcutaneously per day. He was discharged on this regimen. After 3 weeks, the patient had adequate glucose control, NPH was discontinued and metformin was restarted twice daily.

### Case 3

A 78-year-old obese female patient. She has controlled T2DM with an HbA1c of 5.9%. Patient was on metformin only. The patient presented to the ED with a 3-day history of dyspnea and non-productive cough. On admission, the patient's heart rate was 138 b.p.m., respiratory rate was

**Table 1** ABG, electrolytes and serum ketones in patients with DKA and COVID-19.

| | Normal range | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|---|
| pH | 7.35–7.45 | 7.2 | 6.8 | 6.9 | 7.28 | 7.19 |
| $HCO_3$ (mmol/L) | 22–28 | 9.1 | 2.4 | 6 | 12.3 | 7.7 |
| Glucose | | | | | | |
| mmol/L | 3.9–5.5 | 27 | 35 | 34 | 30 | 25 |
| mg/dL | 80–100 | 486 | 625 | 610 | 538 | 445 |
| Osmolarity (mosmol/L) | 275–295 | 290 | 243.7 | 250 | 253 | 256 |
| Calculated anion gap (mEq/L) | 6–12 | 15 | 14 | 16 | 15 | 18 |
| Sodium (mEq/L) | 135–145 | 140 | 143 | 139 | 135 | 142 |
| Potassium (mEq/L) | 3.5–5.5 | 3.9 | 4.3 | 4.2 | 4.5 | 5.4 |
| Choride (mEq/L) | 97–107 | 116 | 127 | 117 | 108 | 117 |
| Serum BHB (mmol/L) | 0.4–0.5 | 5.4 | 6.2 | 5.9 | 5.6 | 5.8 |
| Creatinine (μmol/L) | 0.7–1.2 | 0.6 | 0.45 | 0.5 | 0.43 | 0.67 |

BHB, beta hydroxybutyrate.

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28 cpm, blood pressure was 100/80 mmHg, and oxygen saturation was 80% on room air. ABGs, electrolyte, and serum ketone levels were measured (Table 1). The patient was tested for COVID-19 and a positive result was obtained. She was transferred to the ICU with a diagnosis of severe DKA. Shortly after the transfer, the patient's condition deteriorated, and she was subsequently intubated. Aggressive fluid resuscitation was initiated, along with the administration of insulin drip and broad-spectrum antibiotics. The patient had persistent hypotensive episodes, and she eventually developed acute kidney injury and liver dysfunction leading to multiple organ failure. Despite all efforts, the patient expired on the 3rd hospital day.

### Case 4

A 40-year-old man with T2DM complicated with diabetic nephropathy on insulin NPH 18 units per day with an HbA1c of 6.4%. The patient presented to the ED with fever, myalgia, and cough. He denies polyphagia, polyuria, or abdominal pain. On admission, the patient's heart rate was 90 b.p.m., RR was 27 cpm, and oxygen saturation was 96% on room air. ABGs, electrolyte, and serum ketone levels were measured (Table 1). The patient was also tested for COVID-19 which returned a positive result. The patient was diagnosed with mild DKA and was transferred to the COVID-19 floor. Intravenous fluids were started, and the patient also received an insulin drip during the 1st hospital day. The anion gap closed on the 3rd hospital day, and the patient was eventually discharged and maintained on a new insulin regimen consisting of NPH 22 units per day. At 3 weeks follow up, the patient continued with the same regimen.

### Case 5

A 66-year-old male patient with T2DM on metformin and glibenclamide, with an HbA1c of 7% was transferred from a primary care clinic to the ED with a 5-day history of cough, fever, and shortness of breath. On admission, the patient's HR was 98 b.p.m., RR was 25 cpm, and oxygen saturation was 93% on room air. Serum glucose was 300 mg/dl and 6 units of rapid insulin were administered subcutaneously. The patient was also tested for COVID-19 which returned a positive result. On admission, i.v. fluids were started along with azithromycin, prophylactic enoxaparin, and steroids. On the 2nd hospital day, the patient was observed to have an altered mental status. The patient's vital signs were taken and are as follows: blood pressure of 90/60 mmHg, HR of 100 b.p.m., RR of 30 cpm, and oxygen saturation of 95% on 5 L $O_2$ via a nasal cannula. ABGs, electrolyte, serum ketone (Table 1) were taken. The patient was diagnosed with moderate DKA and was immediately transferred to the ICU. Fluid resuscitation was initiated, along with Cefepime and Vancomycin. Insulin drip was started. Hypotensive episodes prompted norepinephrine administration. The persistence of hypotensive episodes was noted, and despite all efforts, the patient eventually expired.

### Treatment

All patients received regular insulin drip whilst the anion gap was open. For fluid resuscitation, normal saline solution was used. In severe cases of severe DKA (pH < 6.9), a bicarbonate infusion was also added. In addition, all patients received 2 g I.V. ceftriaxone, 500 mg oral azythromicin, and 60 mg enoxaparin as part per our institution's protocol for COVID-19.

### Outcome and follow-up

Three patients were observed to be clinically improved and were eventually discharged. All patients were started on an NPH insulin regimen. Follow-up and monitoring was done up to 3 weeks after discharge in an outpatient clinic, with all patients having adequate glucose control.

## Discussion

We report five T2DM patients with acute hyperglycemic crisis precipitated by COVID-19 as an initial presentation or during the course of hospitalization. SARS-CoV-2 infection was confirmed by real-time RT-PCR. Two patients presented with moderate, two patients presented with severe, and one presented with mild DKA. Two patients expired despite appropriate medical treatment. The ones that expired had other comorbidities and were elderly patients. To the best of our knowledge, this is the largest case series of metabolic dysregulations that trigger DKA precipitated by COVID-19 in South America.

COVID-19 may cause metabolic dysregulations in the entire endocrine system ranging from thyroid disease, adrenal disease, gonadal axis, and especially with the pancreas leading to glucose dysregulations such as diabetes (13).

Diabetes mellitus is a leading cause of mortality and morbidity worldwide. There are several studies demonstrating diabetic patients as high risk for serious

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infections most likely due to an altered immune system (14). Guo *et al*. reported that among patients with SARS-CoV-2 pneumonia patients with diabetes were more severe than those without diabetes evaluated by organ damage, inflammatory factors, or hypercoagulability, and more likely to progress to severe COVID-19 or fatal outcomes (15).

DKA is an acute and life-threatening complication of diabetes mellitus (16). Early recognition and treatment are critical as they can be fatal in some cases (17). Insulin deficiency causes uncontrolled hyperglycemia and results in ketone production and osmotic diuresis, both of which play an important role in DKA (18).

Several viruses have been linked to endocrine metabolic dysregulations. Severe acute respiratory syndrome has been linked to hyperglycemia and DKA. Yang *et al*. reported that out of 39 patients with SARS, 20 developed diabetes during hospitalization (19). In 2009, H1N1 influenza caused a pandemic and metabolic dysregulation was present. Moghadami *et al*. reported 2 fatal cases of DKA precipitated by this infection (20). All of these cases point out that not only bacterial infections may cause DKA but also viruses such as the human herpesvirus HHV-8, varicella zoster virus, HHV-6, herpes simplex virus and Coxsackie B3 virus (21, 22).

Unlike the other viral causes where prevalence is not clear and fewer case reports are available in the literature, prevalence of DKA in COVID-19 may be high according to several previous studies. Nina Goldman *et al*. reported that 4 out of 218 individuals hospitalized with COVID-19 had DKA episodes (1.8%) (23).

Patients with severe COVID-19 were found out to have T2DM. A report from Wuhan, China involving 191 hospitalized patients with COVID-19, T2DM was found to be the second most common comorbidity (19). In a retrospective, longitudinal, multi-centered study from a cohort of 7,337 patients, Zhu *et al*. reported that diabetics with COVID-19 had a higher mortality rate compared with non-diabetics with COVID-19 (7).

Acute hyperglycemic crises, such as DKA, are also directly related to an increase in morbidity and mortality in patients with pre-existing diabetes (24). A recently published paper has reported a case of DKA in a patient with pre-existing diabetes and a case of new-onset diabetes presenting with DKA (25).

The exact mechanism of how COVID-19 may precipitate DKA is not fully understood; however, several explanations have been put forward. COVID-19 may trigger a stress response causing the secretion of hyperglycemic hormones, resulting in an increased risk for DKA (26). SARS-CoV-2 also binds to the angiotensin-converting enzyme-2 (ACE2) receptor found in pancreatic cells, causing a decrease in insulin leading to DKA (19). Furthermore, COVID-19 may theoretically cause a pro-inflammatory state, inducing ketogenesis and increasing the risk for DKA (27). Li *et al*. also reported that COVID-19 may induce the production of ketones leading to ketosis in patients with or without T2DM (28).

In conclusion, COVID-19 may trigger DKA in patients with T2DM as any other viral infection. It may cause acute metabolic dysregulations by an inflammatory syndrome leading to insulin resistance and B cell dysfunction. Clinicians need to be aware of the unexpected development of DKA in COVID-19 patients with a history of T2DM to reduce unfortunate outcomes.

**Declaration of interest**
The authors declared that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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**Patient consent**
Written informed consent was obtained from patients for publication of this article.

**Author contribution statement**
A R Y, R F G, S O R, I S M, and I S A O were involved in patients' care, K M designed the research and extracted data; A R Y, K M, R F G, S O R, I S M, I S A O, and R C wrote the paper.

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