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## Case Report

## Euglycemic Diabetic Ketoacidosis With COVID-19 Infection in Patients With Type 2 Diabetes Taking SGLT2 Inhibitors

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## ABSTRACT

**Objective:** Diabetes mellitus is associated with poor outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Diabetic ketoacidosis (DKA) has also been reported to occur with this virus. A cluster of cases of euglycemic DKA (euDKA) was identified in patients with type 2 diabetes mellitus using sodium-glucose cotransporter-2 inhibitors (SGLT2is) who developed SARS-CoV-2 infection.

**Methods:** The cases were identified by the authors while providing clinical care, and details were collected.

**Results:** Five cases of euDKA, presenting with glucose levels <300 mg/dL, were identified over the course of 2 months by the endocrinology consult service. All patients had a history of type 2 diabetes mellitus with no known history of DKA. All were taking SGLT2is. Oral antihyperglycemic medications were stopped for all patients on admission. All received intravenous insulin infusion to treat DKA before being transitioned to a subcutaneous insulin regimen. SGLT2i use was discontinued for all patients who were discharged.

**Conclusion:** EuDKA has been seen in the setting of acute illness in patients using SGLT2is, but this cluster of cases suggests that there is a specific association with SARS-CoV-2 infection. In addition to the known risk of euDKA with SGLT2i use, coronavirus disease 2019-specific mechanisms may include a direct toxic effect of the virus on the pancreatic islets, an accelerated inflammatory response promoting ketosis, and the diuretic effect of SGLT2i in conjunction with anorexia and vomiting. It is crucial to counsel patients to stop SGLT2is when sick, especially if SARS-CoV-2 infection is suspected.

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## Introduction

Diabetes mellitus is a known risk factor for severe disease<sup>1</sup> and death<sup>2</sup> in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Diabetic ketoacidosis (DKA) has been reported with this virus,<sup>3</sup> as with other severe infections,<sup>4</sup> in patients with both type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM).

**Abbreviations:** COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; euDKA, euglycemic diabetic ketoacidosis; HD, hospital day; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.

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The SARS-CoV-1 virus may have a direct toxic effect on pancreatic islets; infection led to acute diabetes that lasted up to 3 years in some patients but resolved in most.<sup>5</sup> There is speculation that the same could be true for SARS-CoV-2.

We report 5 cases of euglycemic DKA (euDKA) in patients with SARS-CoV-2 infection taking sodium-glucose cotransporter-2 inhibitors (SGLT2is). The first SGLT2is were approved in 2013, and early clinical experience revealed an association with DKA, especially euDKA.<sup>6,7</sup> With recent trials showing improved cardiovascular outcomes in patients taking SGLT2is,<sup>8</sup> their use has become increasingly prevalent. While the U.S. Food and Drug Administration advises discontinuation prior to planned procedures and during illness,<sup>9</sup> there are ongoing clinical trials assessing the drug's impact in hospitalized patients with acute cardiovascular disease,<sup>10</sup> including one designed specifically for those with coronavirus disease 2019 (COVID-19).<sup>11</sup> Our report raises serious concerns that

the risk of taking SGLT2is during illness may be enhanced in the setting of COVID-19.

### Case Report

An unusual cluster of euDKA associated with SGLT2i use was identified by the authors in patients with T2DM who were diagnosed with COVID-19 during the period of peak infection in Boston, Massachusetts. This series was approved by the Institutional Review Board.

#### Results

Five cases diagnosed between March and May 2020 are detailed below. None had a prior history of DKA or any known complications of T2DM, all had antihyperglycemic medications stopped upon admission, and all were treated with intravenous and then subcutaneous insulin after DKA diagnosis. SGLT2is were discontinued after hospitalization.

#### Case 1

A 79-year-old man with T2DM and hypertension presented with shortness of breath, nausea/vomiting, and abdominal pain. His home medications included empagliflozin (10 mg daily), metformin (500 mg twice daily), and lisinopril (2.5 mg daily). He was diagnosed with acute cholecystitis and DKA (Table). He was not tested for COVID-19 on admission, but on hospital day (HD) 12, he had a positive viral polymerase chain reaction (PCR) result for SARS-CoV-2 and required intubation. Although unproven, the hospital's infection control experts felt that he likely had undiagnosed COVID-19 on admission. He was discharged to a rehabilitation facility on HD 47.

#### Case 2

A 52-year-old man with T2DM, hypertension, and nonalcoholic steatohepatitis presented to an outside hospital with fever, cough, and 8 days of dyspnea. His home medications included empagliflozin (25 mg daily), glipizide (10 mg daily), metformin XR (2000

mg nightly), and irbesartan (150 mg daily). SARS-CoV-2 viral PCR test result was positive. He was transferred to our hospital without having received insulin and intubated on arrival. He was found to be in mild DKA (Table). His course was complicated by acute respiratory distress syndrome, and he died on HD 18.

#### Case 3

A 69-year-old male with T2DM, hypertension, and hyperlipidemia presented to an outside hospital with cough, shortness of breath, and anorexia for 3 days. His home medications included empagliflozin (10 mg daily), metformin (1000 mg twice daily), and enalapril (10 mg twice daily). SARS-CoV-2 viral PCR test result was positive. He was intubated for hypoxia and transferred to our hospital. He was initially noted to have mild ketosis, with  $\beta$ -hydroxybutyrate 1.8, arterial pH 7.39, and anion gap 18. Over the next 12 hours, he developed DKA (Table). His course was complicated by multiple reintubations. He was discharged to a rehabilitation facility on HD 33.

#### Case 4

A 53-year-old woman with T2DM and hyperlipidemia presented to an outside hospital with fever and anorexia for 1 week. Her home medications included empagliflozin (10 mg daily), insulin glargine (22 units nightly), exenatide (2 mg weekly), metformin (1000 mg twice daily), and glimepiride (4 mg twice daily). She was found to have a positive SARS-CoV-2 viral PCR result. On admission, her glucose was 57 mg/dL, and home insulin was withheld. She developed mild anion gap metabolic acidosis and DKA 2 days later (Table). She was transferred to our hospital, where acidosis became severe on arrival. She was discharged home on HD 11.

#### Case 5

A 70-year-old woman with T2DM and hypertension presented 8 days after COVID-19 diagnosis with a pulseless foot from arterial thrombosis. Her home medications included canagliflozin (300 mg daily), dulaglutide (1.5 mg weekly), sitagliptin-metformin (50-1000 mg twice daily), and losartan and hydrochlorothiazide (dosages unknown). Her initial laboratory parameters revealed DKA (Table).

**Table**  
Case Details

Case	1	2	3	4	5
Age (y)	79	52	69	53	70
Sex	Male	Male	Male	Female	Female
T2DM duration (y)	17	14	Unknown	15	Unknown
BMI (kg/m <sup>2</sup> )	28.9	28.3	30.7	24.0	32.4
Admission month	March 2020	April 2020	April 2020	April 2020	May 2020
Prior HbA1C (%; mmol/mol), (mo/y)	7.8, 62 (February 2020)	7.9, 63 (October 2018)	7.3, 56 (April 2020)	6.7, 50 (January 2020)	7.9, 63 (May 2020)
SGLT2i dose	Empagliflozin 10 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Empagliflozin 10 mg	Canagliflozin 300 mg
Insulin dose prior to DKA	none	none	none	glargine 22 units nightly	None
Potential contributors	COVID-19, cholecystitis, vomiting	COVID-19, anorexia	COVID-19, anorexia	COVID-19, anorexia	COVID-19, ischemic foot, anorexia
Plasma glucose when DKA diagnosed (mg/dL)	286	146	166	151	190
pH	7.16 (venous)	7.30 (venous)	7.31 (venous)	7.27 (arterial)	7.09 (arterial)
pCO <sub>2</sub>	22	39	43	19	40
Bicarbonate (mmol/L)	5	15	20	5	10
Lactate (mmol/L)	2.4	2.1	1.1	1.5	1.5
Anion gap	40	23	20	30	20
$\beta$ -Hydroxybutyrate (mmol/L)	11.2	4.9	3.0	5.9	5.3
Creatinine (mg/dL)	1.20	0.86	0.80	0.85	0.73
eGFR (mL/min/1.73 m <sup>2</sup> )	57	100	91	78	83
Clinical outcome	Discharged to rehabilitation facility	Died	Discharged to rehabilitation facility	Discharged home	Discharged to rehabilitation facility

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HbA1C = glycated hemoglobin; SGLT2i = sodium-glucose cotransporter-2 inhibitors; T2DM = type 2 diabetes mellitus.

Patient characteristics and laboratory values of 5 patients with COVID-19 and euglycemic DKA. Laboratory values reflect the day of presentation at our institution unless otherwise noted in the text. None of the patients received insulin or other DKA-directed therapy prior to presentation at our institution.

Her DKA resolved on HD 2 but recurred on HD 4, requiring reinitiation of insulin infusion. She underwent revascularization of her lower extremity and was discharged to a rehabilitation facility on HD 28.

## Discussion

We describe a cluster of 5 cases of euDKA in patients with T2DM admitted to our hospital with COVID-19 during the height of the pandemic locally, all of whom were taking SGLT2is prior to admission.

EuDKA was first described in 1972, when Munro et al reported 37 cases of patients with type 1 diabetes mellitus who developed severe DKA with a glucose level <300 mg/dL;<sup>12</sup> it has more recently been defined as DKA with a glucose level <250 mg/dL.<sup>13</sup> SGLT2is have a known association with euDKA, with more cases in patients with T2DM seen in real-world practice than in clinical trials.<sup>6,13</sup> In a retrospective cohort study, patients with diabetes using SGLT2is had an odds ratio of 1.48 for DKA compared with nonusers, and 41% of these patients had a peak glucose level of <250 mg/dL compared with 0.8% of nonusers.<sup>7</sup> Known precipitating factors include acute illness with poor oral intake, vomiting, fasting, and reductions in insulin doses;<sup>14</sup> all our patients reported such factors.

The increased risk of DKA in COVID-19 may be synergistic with the risk conferred by SGLT2i use, which could explain this cluster of cases. Mechanisms underlying DKA, including increased hepatic glucose production, free fatty acid-related insulin resistance, and unchecked lipolysis,<sup>15</sup> may be exacerbated with concurrent use of SGLT2is in the setting of acute illness. In addition, SGLT2i are diuretics, and their use could worsen volume depletion and starvation ketosis.

Most patients with SGLT2i-associated DKA in the study by Hamblin et al were also taking insulin,<sup>7</sup> which is true of only 1 of our patients. This difference suggests that a unique feature of COVID-19 may have further predisposed our patients to DKA. Increased incidence of new-onset diabetes and DKA has been seen in the COVID-19 pandemic,<sup>16</sup> which researchers are now tracking using a registry.<sup>17</sup> A direct toxic effect of the SARS-CoV-2 virus on pancreatic islets, as seen with SARS-CoV-1, could contribute. Pancreatic islets show increased expression of angiotensin-converting enzyme 2 receptors, which may lead to a higher rate of cell death among insulin-producing cells,<sup>5</sup> decreased endogenous insulin production, and increased likelihood of DKA. Elevations in proinflammatory cytokines, such as interleukin 6, are seen in severe COVID-19 infections.<sup>18</sup> This response may also contribute to ketoacidosis; interleukin 6 has been implicated in hyperglycemia induced by physiologic stress, and the elevation is even higher in patients with impaired glucose tolerance.<sup>16,19</sup> Thus, a cytokine storm is another mechanism that potentially contributes to the increased incidence of euDKA in patients with COVID-19 taking SGLT2is.

This study is limited as an observational case series with no comparator group. While we do not have data on the baseline frequency of euDKA within our hospital prior to the pandemic, our diabetes inpatient service is generally consulted for unusual cases of DKA. The service has consulted on fewer than 10 inpatient cases of SGLT2i-associated euDKA in the last 24 months. Five cases in 2 months (3 within 1 week) represents an unusually high incidence. Further limitations include the fact that several of the patients presented from outside hospitals and they may have received therapies such as insulin that were undocumented in the transfer paperwork. Finally, the glucose level in case 1 was 286 mg/dL, but his degree of acidosis was disproportionate to this level of hyperglycemia.

Some of our patients had evidence of mild anion gap metabolic acidosis for several days before developing severe DKA. The diagnosis of euDKA is often missed or delayed due to the absence of hyperglycemia. SGLT2is can impact glucose excretion for up to 10 days after they are discontinued,<sup>20</sup> which could lead to delayed DKA as demonstrated in case 4. The date when SGLT2is were last used is not known for every case, but despite these patients having symptoms for several days prior to admission, none reported withholding their SGLT2i. Clinicians must maintain a high index of suspicion of euDKA in patients with COVID-19 who have taken an SGLT2i.

## Conclusion

These cases highlight the potential increased danger of SGLT2i use in acute illness with COVID-19. While they may simply reflect increased SGLT2i use and prevalent critical illness in the COVID-19 pandemic, we suggest a plausible physiologic mechanism for increased DKA incidence. All patients taking SGLT2is should be counseled to stop this medication if they become ill or have poor intake. The marked hyperglycemia often seen in COVID-19 and the increased risk of severe disease among those with cardiovascular disease suggest SGLT2is as a potential therapy during active infection. However, our experience suggests that the potential for serious harm may outweigh the possible benefits, and the current practice to avoid these medications during illness remains prudent.

## Author Contributions

R.J.V. and Y.K.V. contributed equally to this work.

## Disclosure

The authors have no multiplicity of interest to disclose.

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