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## Case Series

## Euglycemic Diabetic Ketoacidosis Caused by SGLT2 Inhibitors and a Ketogenic Diet: A Case Series and Review of Literature

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## ABSTRACT

**Objective:** Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively novel class of oral medications for the treatment of type 2 diabetes mellitus (T2DM). Their use has increased recently due to their beneficial renal and cardiovascular outcomes, but they come with the rare risk of diabetic ketoacidosis (DKA) at normal or slightly elevated glucose values, termed euglycemic DKA (euDKA). Recently, carbohydrate-deprived, ketogenic diets have gained popularity due to benefits of weight loss and improved control of T2DM. We describe 2 patients with T2DM who developed euDKA caused by SGLT2 inhibitor use while on a ketogenic diet and provide a review of the literature.

**Methods:** We describe the hospital course, laboratory data, and treatment of 2 patients and provide a literature review.

**Results:** Both of our patients were found to have normal or mildly elevated serum glucose levels, with an elevated anion gap and ketosis, representative of euDKA. The first patient developed euDKA after only 1 dose of empagliflozin, while the second patient developed euDKA after only 1 week of being on a ketogenic diet while on an SGLT2 inhibitor.

**Conclusion:** While there have been a few reports of euDKA with SGLT2 inhibitors and ketogenic diets, many physicians prescribing these medications may not be aware of this association. Therefore, they must inform their patients to avoid a ketogenic diet if on an SGLT2 inhibitor. If a patient presents with symptoms of DKA and is eating a carbohydrate-free diet while taking an SGLT2 inhibitor, there should be a low threshold to screen for DKA.

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## Introduction

Diabetic ketoacidosis (DKA), a metabolic complication commonly seen in patients with type 1 diabetes mellitus (T1DM), also occurs in patients with T2DM. It is caused by an insulin deficiency and an increase in counter-regulatory stress hormones, including glucagon, leading to hyperglycemia, ketosis, and electrolyte abnormalities.<sup>1</sup> EuDKA is DKA with normal or mildly elevated serum glucose levels and is defined by the Food and Drug Administration as a serum glucose level of  $\leq 250$  mg/dL.<sup>2,3</sup> SGLT2

inhibitors were approved in 2013 for the treatment of T2DM.<sup>4</sup> These agents cause glycosuria and increase the production of ketones by switching from glucose to lipid utilization. A ketogenic diet, low-carbohydrate, high-fat, or moderate-protein diet can also shift the body toward ketosis because the body begins to break down fats as a source of energy.<sup>5</sup> The Food and Drug Administration issued warnings for SGLT2 inhibitors, including an increased risk for ketoacidosis, urinary tract infections, and amputations.<sup>3,6</sup> A review of SGLT2 inhibitor-associated ketoacidosis revealed that 71% of the cases were euDKA.<sup>2</sup> We present 2 cases of euDKA in patients using SGLT2 inhibitors and on ketogenic diets.

## Case 1 Presentation

A 47-year-old woman with a past medical history of T2DM diagnosed 2 months prior to admission, hyperlipidemia, and obesity who presented to the emergency department with acute-onset left-arm numbness and chest pain and a few months history of polyuria and polydipsia. She had been prescribed metformin

**Abbreviations:** DKA, diabetic ketoacidosis; euDKA, euglycemic DKA, decarboxylase; HbA1C, hemoglobin A1C; SGLT2, sodium-glucose cotransporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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500 mg twice daily, empagliflozin 25 mg daily, and linagliptin 5 mg daily. The day prior to admission, she took her first and only dose of empagliflozin, an SGLT2 inhibitor. She had been on a low-carbohydrate diet for 2 months. On presentation, the patient's plasma glucose level was 187 mg/dL, bicarbonate level was 11 mmol/L, anion gap level was 22 mmol/L,  $\beta$ -hydroxybutyrate level was 6.78 mmol/L, hemoglobin (Hb) A1C level was 13.6% (125 mmol/mol International Federation of Clinical Chemistry units), and her venous blood gas pH was 7.24. Cardiac causes of chest pain were ruled out, with negative troponins, normal electrocardiogram, and chest X-ray. Her laboratory results were consistent with euDKA. The patient was admitted to the intensive care unit and was placed on an insulin drip and dextrose drip per the hospital DKA protocol, requiring the insulin drip for 5 days prior to resolving her acidosis. The patient was discharged on glargine, lispro, and metformin. She was told to discontinue empagliflozin.

### Case 2 Presentation

A 34 year-old-man with a past medical history of T2DM diagnosed >5 years prior to presentation, hypertension, hyperlipidemia, and obesity presented to the emergency department with 1 day of chest pain associated with shortness of breath. His home diabetes regimen included canagliflozin 100 mg daily, started 2 months previously, and subcutaneous dulaglutide 0.5 mL every 7 days. He was not on metformin because of a drug allergy. He had started a ketogenic diet a week before presentation. On presentation, her laboratory tests revealed a serum glucose level of 251 mg/dL, bicarbonate level of 12 mmol/L, anion gap level of 24 mmol/L,  $\beta$ -hydroxybutyrate level of 5 mmol/L, HbA1C level of 8.2% (66 mmol/mol International Federation of Clinical Chemistry units), venous blood gas pH of 7.27, D-dimer level of 380 ng/mL, and negative troponins. The electrocardiogram showed sinus tachycardia and a subsequent workup, including an echocardiogram, nuclear stress test, and a computed tomography angiogram, ruled out a cardiac or pulmonary etiology. The patient was admitted to the intensive care unit for euDKA and placed on an insulin drip and dextrose drip. The hospital protocol required the insulin drip for 3 days before resolving the acidosis. The patient was discharged on dulaglutide and glargine and was advised to discontinue canagliflozin.

### Discussion

The duration of treatment with an SGLT2 inhibitor before the onset of DKA varies in reports from 0.3 to 420 days.<sup>7</sup> Interestingly, in both our patients, euDKA took 3 or more days to resolve. Studies

have shown that euDKA generally takes twice as long to resolve as classic DKA, 92 hours versus 35 hours, respectively.<sup>8</sup> The underlying etiology of this prolonged acidosis is still unclear. SGLT2 inhibitors have gained popularity because of their renal and cardiovascular benefits. These agents reduce the risk of major adverse cardiac outcomes by 11% in patients with a history of atherosclerotic cardiovascular disease, cardiovascular death or hospitalization for heart failure by 23%, and progression of renal disease by 45%.<sup>9</sup> Other benefits include weight loss, increased high-density lipoprotein levels, and a small decrease in blood pressure.<sup>10</sup> Adverse effects include genital and urinary tract infections, volume depletion, acute kidney injury, bone fractures, Fournier's gangrene, lower extremity amputations, and DKA.<sup>3,6,10,11</sup>

SGLT2 inhibitors have been used off-label in patients with T1DM.<sup>1</sup> SGLT2 inhibitor-associated DKA in T1DM has a rate of 5% to 12%, compared with <0.1% in T2DM.<sup>1</sup> Another study determined that one third of all DKA cases may be attributed to T2DM.<sup>12</sup> Precipitating factors leading to SGLT2 inhibitor-associated DKA include insulin reduction, omission, or deficiency along with surgery, alcohol abuse, exercise, and low-carbohydrate diets.<sup>1,7</sup> SGLT2 inhibitors inhibit glucose reabsorption by proximal renal tubules and lead to a switch from glucose to lipid utilization, thereby increasing production of ketones in the liver by increasing glucagon and decreasing the insulin-glucagon ratio. This leads to ketogenesis, gluconeogenesis, and glycogenolysis.<sup>1,13</sup> SGLT2 inhibitors may cause glucagon secretion by a direct effect on pancreatic  $\alpha$ -cells and also reduce renal ketone body clearance.<sup>13,14</sup> The near normal blood glucose levels seen in euDKA caused by SGLT2 inhibitors results from a balance between endogenous glucose production and renal glucose clearance.<sup>1</sup> The pathophysiology of classic DKA is similar to that of euglycemic DKA, however the latter occurs with near normal or slightly elevated blood glucose levels, which often results in a delay in diagnosis. Similarly, with ketogenic diets there is an inadequate supply of carbohydrates, thus the body begins to burn fats for energy, which are then converted into fatty acids and ketones in the liver. In the 1920s ketogenic diets were used to treat drug-resistant childhood epilepsy. Since then, the diet has been studied in neurodegenerative diseases including Alzheimer's and Parkinson's disease because of its neuroprotective effects.<sup>5</sup> Novel benefits of the ketogenic diet include better control of T2DM. In some reports, patients with T2DM experienced a 34% reduction of HbA1C, lower triglyceride levels, increased high-density lipoprotein levels, and weight loss in the first year of a low-carbohydrate diet compared with those on high-carbohydrate diets.<sup>15,16</sup> Risks of ketogenic diets include nausea, vomiting, malnutrition, pancreatitis, hypoglycemia, osteopenia, nephrolithiasis, and cardiomyopathy.<sup>5</sup>

**Table**  
Reported Cases of SGLT2 Inhibitor Use Associated With euDKA and Low-Carbohydrate Diets in Patients With T2DM

Patient age (y)	Gender	Number of years patient had T2DM	Number of days on a low-carbohydrate diet before developing euDKA	Number of days patient took SGLT2 inhibitor before developing euDKA	Plasma blood glucose (mg/dL) on admission to the hospital for euDKA	HbA1C at the time of admission for euDKA	Number of days patient required insulin drip	Reference
32	Female	22	~3960	13	191	9.3% (78 mmol/mol IFCC)	Unknown	17
44	Male	16	Unknown	3–4	180	9.3% (78 mmol/mol)	Unknown	18
64	Female	Unknown	60	365	~185.59	7.5% (58 mmol/mol IFCC)	Unknown	19
73	Male	10	7	Unknown	Unknown	Unknown	Unknown	20
					Point-of-care blood glucose: 143			
31	Female	Unknown	14	Unknown	139	Unknown	Unknown	21
34 <sup>a</sup>	Male	>5	7	~60	251	HbA1C 8.2% (66 mmol/mol IFCC)	3	
47 <sup>a</sup>	Female	~0.17	~60	1	187	HbA1C 13.6% (125 mmol/mol IFCC)	5	

Abbreviations: euDKA = euglycemic diabetic ketoacidosis; HbA1C = hemoglobin A1C; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

<sup>a</sup> Patient case 1 and 2 from our report included for comparison.

To date, few cases have been reported of euDKA associated with SGLT2 inhibitor use and ketogenic diets in patients with T2DM. Table compares and contrasts cases reported in literature.<sup>17–21</sup> To our knowledge, our case is the first report of euDKA occurring after just 1 dose of an SGLT2 inhibitor while on a ketogenic diet. Table indicates the number of days a patient received an SGLT2 inhibitor before developing euDKA, which ranged from 1 day (our study) to 365 days. It also shows the number of days a patient was on a low-carbohydrate diet before developing euDKA, which ranged from 7 to 3960 days. Additionally, both our patient cases demonstrate the prolonged need for insulin in such a setting (3 and 5 days). Many previously reported cases do not mention this. Of note, glutamic acid decarboxylase antibodies and islet antigen-2 antibodies were not assayed in either case. It is possible that these patients could have had a missed diagnosis of T1DM or latent autoimmune diabetes. A previous study showed that 22% of patients who presented with DKA were misdiagnosed with T2DM and had T1DM or latent autoimmune diabetes.<sup>22</sup> In addition, in patient case 2, the glucose level was 251 mg/dL, which was near the cutoff level for a diagnosis of euDKA, which is a glucose concentration of <250 mg/dL.

Patients should maintain an appropriate carbohydrate-controlled diet while taking an SGLT2 inhibitor, given the increased risk for DKA. To prevent SGLT2 inhibitor-associated DKA, these agents should be withheld in circumstances that may trigger DKA including infection, 3 days prior to surgery, excessive alcohol use, or dehydration.<sup>1,3</sup>

## Conclusion

Recently, the increased use of ketogenic diets has been accompanied by reports of patients admitted to the hospital for euDKA in the setting of SGLT2 inhibitor use while on a ketogenic diet. If a patient on an SGLT2 inhibitor and ketogenic diet presents with mildly elevated glucose levels, ketosis, and an elevated anion gap, euDKA should be suspected and included in the differential diagnosis. Patients taking SGLT2 inhibitors should be advised to avoid a ketogenic diet. If a patient develops euDKA in the setting of SGLT2 inhibitor use and a ketogenic diet, the SGLT2 inhibitor should be stopped and avoided in the future.

## Disclosure

The authors have no multiplicity of interest to disclose.

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