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# Life-Threatening Complications Related to Delayed Diagnosis of Euglycemic Diabetic Ketoacidosis Associated with Sodium-Glucose Cotransporter-2 Inhibitors: A Report of 2 Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Conflict of interest:** None declared

**Case series**
**Patients:** Female, 52-year-old • Female, 76-year-old
**Final Diagnosis:** Euglycemic diabetic ketoacidosis • myocardial infarction • sinus node dysfunction
**Symptoms:** Unconsciousness • vomiting
**Medication:** —
**Clinical Procedure:** Hemodialysis • pacemaker insertion
**Specialty:** Critical Care Medicine • Endocrinology and Metabolic

**Objective:** Unusual clinical course

**Background:** Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are widely used owing to their effective glycemic control and protective effects against heart and kidney failure. Euglycemic diabetic ketoacidosis (eu-DKA) is a complication of treatment with SGLT2is. Eu-DKA often leads to delayed diagnosis and results in life-threatening complications. We report 2 critical cases of SGLT2i-associated eu-DKA.

**Case Reports:** Case 1 was 52-year-old woman with unstable angina scheduled for elective coronary artery bypass grafting surgery. Preoperatively, she underwent tooth extraction which led to poor food intake because of pain. Three days before surgery, the patient had SGLT2i-associated eu-DKA and myocardial infraction, requiring percutaneous coronary intervention and peripheral venoarterial extracorporeal membrane oxygenation. The patient had taken SGLT2i until the morning of admission to the intensive care unit.

Case 2 was a 76-year-old woman experiencing SGLT2i-associated eu-DKA and sinus arrest, necessitating a temporary pacemaker, followed by elective gastrojejunal bypass surgery. The SGLT2i was discontinued the day before surgery. On day 3 following surgery, the patient's metabolic acidosis improved, and sinus arrest resolved.

**Conclusions:** Precipitating factors of eu-DKA (caloric restriction and surgical stress) and delay in diagnosis because of a lack of evidence of hyperglycemia could contribute to the development and worsening of life-threatening complications. This reiterates the importance of reviewing ongoing medications of patients with diabetes and considering eu-DKA as a differential diagnosis for patients with high anion gap metabolic acidosis to ensure early intervention. SGLT2i-associated DKA likely develops perioperatively; therefore, clinicians should pay attention to the discontinuation period of SGLT2i before any surgical intervention.

**Keywords:** Diabetes Complications • Diabetic Ketoacidosis • Sodium-Glucose Transport Proteins

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## Background

Sodium-glucose cotransporter-transporter-2 inhibitors (SGLT2is) are used widely owing to their protective effects against heart and kidney failure and effective glycemic control [1-6]. SGLT2is decrease glycated hemoglobin, body weight, and blood pressure [1,2]. Recent randomized control trials have demonstrated that SGLT2is reduce the risk of heart failure, cardiovascular death, and serious renal outcomes in patients with or without diabetes [4-6]. However, diabetic ketoacidosis (DKA) has been reported as a complication of SGLT2is [7,8]. It was reported that, compared with dipeptidyl peptidase-4 inhibitors, SGLT2is have a higher risk of DKA (hazard ratio, 2.85) [7]. Caloric restriction, surgical stress, acute illness, risk of dehydration, and medication changes have been reported as precipitating factors of SGLT2i-associated DKA, and nausea and vomiting have been reported as its clinical presentation [9-11]. The incidence of SGLT2i-associated DKA perioperatively has been reported to be as high as 19% to 28% [12,13]. In a review of 47 cases of perioperative SGLT2i-associated DKA, 4 cases of severe acidemia or metabolic acidosis were reported (pH <7.0 in 2 cases; bicarbonate [$HCO_3^-$] level <5 mEq/L in 2 cases) [10]. Unlike with typical DKA, some patients have a normal blood glucose level. This type of DKA is known as euglycemic DKA (eu-DKA). Eu-DKA sometimes leads to delayed diagnosis and results in life-threatening complications [8,9]. Because the use of SGLT2i is expected to become increasingly widespread owing to its effectiveness, it is important to report this adverse drug reaction that can delay diagnosis.

We encountered 2 severe cases of SGLT2i-associated eu-DKA caused by delayed diagnosis in the intensive care unit (ICU). Both patients consented to the publication of this case report.

## Case Reports

### Case 1

A 52-year-old woman weighing 51 kg and receiving medications for type 2 diabetes mellitus (empagliflozin 10 mg daily and sitagliptin 50 mg daily), dyslipidemia (ezetimibe 10 mg daily and rosuvastatin 20 mg daily), and an old cerebral infarction (clopidogrel 75 mg daily) was diagnosed with unstable angina. She was scheduled for elective coronary artery bypass grafting surgery. Following hospital admission, the patient underwent a preoperative examination for the surgery. On days 12 and 15 of admission, she underwent tooth extraction for perioperative management. Subsequently, her oral food intake decreased because of pain. On day 22 of hospitalization, 3 days before the scheduled elective coronary artery bypass grafting surgery, she developed tachypnea, vomiting, and decreased blood pressure. She had high anion gap metabolic acidosis (pH, 6.84; $HCO_3^-$ level, 2.1 mEq/L; base excess, -20.0 mmol/L; anion gap, 31.9 mmol/L; and lactate level, 2.4 mmol/L), while her blood glucose remained at normal levels (178 mg/dL). Empagliflozin was administered until the morning of that day. Although elevated cardiac troponin levels (serum troponin I, 324.5 pg/mL) were detected, no ST-segment elevation was observed on the electrocardiogram. Supportive therapy to manage metabolic acidosis was initiated. She was intubated for hypotension (systolic artery pressure, 78 mmHg; infusion with noradrenaline 0.06 μg/kg/h), severe acidemia, and tachypnea. The oral administration of empagliflozin was discontinued. Despite sodium bicarbonate infusion and continuous renal replacement therapy instituted for the life-threatening acidemia, the patient's metabolic acidosis did not improve. On day 2 of ICU admission, based on elevated blood β-hydroxybutyrate levels (12.9 mmol/L), dextrose and insulin were administered to manage the eu-DKA. The acidosis was resolved within 24 h of treatment initiation; in addition, blood β-hydroxybutyrate levels decreased (4.3 mmol/L). On day 3 of ICU admission, she developed pulmonary edema but still required large doses of inotropes and vasopressors. As the metabolic acidosis improved, the status of her coronary arteries was evaluated. Following insertion of a percutaneous mechanical circulatory support device (Impella 2.5; Abiomed, Danvers, MA, USA) to ensure left ventricular unloading, percutaneous coronary intervention was performed. Stents were placed at 3 points, including the left anterior descending artery. Subsequently, there was a need for peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO) owing to the prevailing potentially life-threatening poor oxygenation (ratio of arterial oxygen partial pressure to fractional inspired oxygen was 57.5 under 10 $cmH_2O$ positive end-expiratory pressure) and low output syndrome. VA-ECMO, continuous renal replacement therapy, Impella 2.5, and mechanical ventilation were required for 6, 6, 7, and 13 days, respectively. In addition, she had a hemorrhagic cerebral infarction on day 10 of ICU admission. She was discharged from the ICU on day 15 and transferred to a rehabilitation hospital on day 51 of admission.

### Case 2

A 76-year-old woman weighing 63 kg and receiving medications for type 2 diabetes mellitus (canagliflozin 100 mg daily and metformin 500 mg daily), hypertension (cilnidipine 20 mg daily), and dyslipidemia (fenofibrate 80 mg daily) was diagnosed with duodenal cancer and scheduled for elective gastrojejunal bypass surgery. Canagliflozin was administered until the day before the surgery. After surgery, she was admitted to the ICU for postoperative management. On arrival, she had euglycemia (100 mg/dL), but with metabolic acidosis (pH, 7.25; $HCO_3^-$ level, -17.3 mEq/L; base excess, -9.1; anion gap, 16.2 mmol/L; and lactate level, 0.8 mmol/L). Sodium





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bicarbonate infusion was initiated; however, the patient's metabolic acidosis continued to worsen. On day 2 of ICU admission, she had cardiac sinus arrest and experienced loss of consciousness with metabolic acidosis (pH, 7.27; $HCO_3^-$ level, 13.5 mEq/L; base excess, -12.1; anion gap, 23.7 mmol/L; and lactate level, 1.1 mmol/L). Elevated blood β-hydroxybutyrate (18.6 mmol/L) levels were noted, and an infusion of dextrose and insulin was initiated for the management of eu-DKA. Within 2 h of initiating eu-DKA treatment, she had another cardiac sinus arrest, lost consciousness, and continued to experience metabolic acidosis (pH, 7.30; $HCO_3^-$ level, 16.0 mEq/L; base excess, -9.3; anion gap, 18.0 mmol/L; and lactate level, 1.0 mmol/L). Coronary angiography showed no myocardial ischemia, and a temporary pacemaker was intravenously inserted as an emergency intervention. On day 3 of ICU admission, the patient's metabolic acidosis improved, her blood β-hydroxybutyrate level decreased (3.2 mmol/L), and sinus arrest resolved. The patient was discharged from the ICU on day 5. Glycosuria was also observed on day 6 (blood glucose level, 140 mg/dL) but was not observed on day 12 (blood glucose level, 163 mg/dL). The temporary pacemaker was removed on day 11, and no signs of sinus arrest were detected using a 24-h Holter monitor on day 14. She was discharged from the hospital on day 18.

## Discussion

We encountered 2 cases of life-threatening complications caused by SGLT2i-associated eu-DKA. Precipitating factors of eu-DKA (caloric restriction and surgical stress) and delay in diagnosis due to lack of evidence of hyperglycemia could have contributed to the development and deterioration of the life-threatening complications in our patients.

The underlying condition leading to eu-DKA was a caloric restriction in case 1 and surgical stress in case 2, and these conditions might have contributed to the development and worsening of life-threatening complications. Preoperative fasting, very low-calorie diets, and surgical stress are reported as precipitating factors of SGLT2i-associated DKA [10,11]. In case 1, tooth extraction resulted in poor food intake, whereas in case 2, DKA developed after surgery. Persistent glycosuria induced by SGLT2i lowers the amount of the body glucose pool [14], and in this situation, when caloric intake decreases, the blood glucose level cannot be increased, insulin secretion is suppressed, and ketone body production is induced. Surgical stress increases counter-regulatory hormones such as adrenaline and cortisol, and these hormones induce increased insulin resistance [10]. Increased insulin resistance causes impaired sugar utilization and ketogenesis. Additionally, surgical stress induces glucagon secretion [10]. Glucagon promotes lipolysis and fatty acid oxidation in the liver and increases ketogenesis [15].

In case 1, it remained unclear whether DKA or myocardial ischemia occurred first. In this patient, tooth extraction resulted in poor food intake; therefore, DKA might have developed before the myocardial ischemia. Several studies have illustrated that acute metabolic acidosis can have critical effects on the cardiovascular system [16,17]. The cardiovascular effects of acidosis include arterial vasodilatation contributing to hypotension [18], a decrease of contractility and cardiac output [19,20], sinus dysfunction [21], and a predisposition to cardiac arrhythmias associated with sudden death [22]. The patient in case 1 had severe coronary artery disease requiring coronary artery bypass grafting. Acidemia due to eu-DKA caused peripheral vasodilation, resulting in hypotension and decreased cardiac contractility due to increased left ventricular end-diastolic pressure. This potentially reduced coronary perfusion pressure and led to the myocardial infarction. Another possible association with DKA and acute coronary syndrome includes the supply-demand mismatch caused by an increased oxygen demand in the myocardium by counter-regulatory hormones, such as adrenaline, cortisol, and glucagon, released during DKA [23].

The patient in case 2 underwent major surgery, and the surgical stress resulted in SGLT2i-associated eu-DKA. A few cases of life-threatening complications due to SGLT2i-associated DKA in the postoperative period have been reported [24,25]. A postoperative gastric bypass case of SGLT2i-associated DKA requiring mechanical ventilation and hemodialysis was reported [24]. A patient that developed SGLT2i-associated DKA 2 days after laparoscopic appendectomy also developed encephalopathy and required mechanical ventilation and hemodialysis [25]; however, there are few reports on patients with severe complications requiring urgent pacemaker insertion for sinus arrest, as in our case 2. Sinus dysfunction and sudden death have been reported to be associated with metabolic acidosis [18,21]. Additionally, in case 2, coronary artery stenosis was not detected on coronary angiography. Once the acidemia improved, the sinus arrest resolved, with a Holter electrocardiogram reaffirming this result. Therefore, we believe that acidemia was the probable cause of the sinus arrest.

Delayed diagnosis due to lack of evidence of hyperglycemia may have contributed to the development of life-threatening complications in our patients. Although SGLT2i has become widely used in recent years, its complication, eu-DKA, appears to be under-recognized, especially by surgeons. Furthermore, eu-DKA often results in blood glucose levels below 200 mg/dL, which may delay its detection [8,9]. Even our cases were followed up with supportive therapy without an accurate diagnosis of metabolic acidosis. Therefore, SGLT2i-associated eu-DKA should be considered a probable differential diagnosis in patients with diabetes and metabolic acidosis. Furthermore, SGLT2i was not discontinued in both of our cases. Because case 1 was an emergency, ongoing medications could not





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be terminated, while in case 2, canagliflozin was discontinued the day before the surgery. Generally, elimination from the body takes about 5 times as long as the half-life of the drug. The average half-life time of canagliflozin is reported to be 10.2 h, and 5 times the half-time is 51 h. The U.S. Food and Drug Administration in 2020 announced the approval of a change in the prescription of SGLT2i diabetes medicines, thereby recommending them to be terminated temporarily 3 or 4 days before scheduled surgery to prevent perioperative SGLT2i-associated ketoacidosis [26]. In our case 2, glycosuria was still detected on day 6 (7 days after the last oral administration of canagliflozin). We believed that the effect of canagliflozin remained at least until that time. In SGLT2i-associated DKA, glycosuria persisted for 3 to 10 days after the discontinuation of SGLT2is [27]. In case 2, canagliflozin may have required a washout period longer than 3 days.

## Conclusions

We reported 2 cases of life-threatening complications that were caused or worsened by SGLT2i-associated eu-DKA. Precipitating factors of eu-DKA (caloric restriction and surgical stress) and delayed diagnosis due to lack of evidence of hyperglycemia may have contributed to the development and worsening of these life-threatening complications. In situations in which SGLT2i is expected to become increasingly widespread owing to its effectiveness, the number of SGLT2i-associated DKA is expected to increase. It is imperative to assess the existing medication history of patients with diabetes and consider eu-DKA as an important differential diagnosis of patients with high anion gap metabolic acidosis to ensure early intervention. Additionally, SGLT2i-associated DKA is likely to develop perioperatively; therefore, clinicians should pay attention to the discontinuation period of SGLT2i prior to any surgical intervention.

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### Department and Institution Where the Work Was Performed

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### Conflict of Interest

None.

## References:

1. Scheen AJ. Reduction in HbA1c with SGLT2 inhibitors vs DPP-4 inhibitors as add-ons to metformin monotherapy according to baseline HbA1c: A systematic review of randomized controlled trials. Diabetes Metab J. 2020;46:186-96
2. Tentolouris A, Vlachakis P, Tzeravini E, et al. SGLT2 inhibitors: A review of their antidiabetic and cardioprotective effects. Int J Environ Res Public Health. 2019;16:27
3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-306
4. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA. 2020;323:1353-68
5. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-46
6. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413-24
7. Douros A, Lix LM, Fralick M, et al. Sodium-glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: A multicenter cohort study. Ann Intern Med. 2020;173:417-25
8. Musso G, Saba F, Cassader M, Gambino R. Diabetic ketoacidosis with SGLT2 inhibitors. BMJ. 2020;371:4
9. Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. Eur J Intern Med. 2019;63:9-14
10. Thiruvenkatarajan V, Meyer EJ, Nanjappa N, et al. Peri-operative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors: A systematic review. Br J Anaesth. 2019;123:27-36
11. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. Clin Ther. 2016;38:2654-64
12. Burke KR, Schumacher CA, Harpe SE. SGLT2 inhibitors: A systematic review of diabetic ketoacidosis and related risk factors in the primary literature. Pharmacotherapy. 2017;37:187-94
13. Bonora BM, Avogaro A, Fadini GP. Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: An updated review of the literature. Diabetes Obes Metab. 2018;20:25-33
14. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care. 2015;38:1638-42
15. Milder DA, Milder TY, Kam PCA. Sodium-glucose co-transporter type-2 inhibitors: Pharmacology and peri-operative considerations. Anaesthesia. 2018;73:1008-18
16. Kraut JA, Madias NE. Metabolic acidosis: Pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010;6:274-85
17. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: A pathophysiologic approach. Nat Rev Nephrol. 2012;8:589-601
18. Kellum JA, Song MC, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest. 2004;125:243-48
19. Wildenthal K, Mierzwiak DS, Myers RW, Mitchell JH. Effects of acute lactic acidosis on left ventricular performance. Am J Physiol. 1968;214:1352-59
20. Mitchell JH, Wildenthal K, Johnson RL Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int. 1972;1:375-89
21. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. Circulation. 2019;140:E333-81
22. Orchard CH, Cingolani HE. Acidosis and arrhythmias in cardiac muscle. Cardiovasc Res. 1994;28:1312-19
23. Jeremias A, Gibson CM. Narrative review: Alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. Ann Intern Med. 2005;142:786-91
24. Hoenes C, Rashid Q, Pimentel J. Diabetic ketoacidosis in a postoperative gastric bypass patient. Int J Surg Case Rep. 2017;2017:rjx148





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25. Gelaye A, Haidar A, Kassab C, et al. Severe ketoacidosis associated with canagliflozin (Invokana): A safety concern. Case Rep Crit Care. 2016;2016:1656182
26. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. FDA Drug Safety Communication, 2015, *http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm*
27. Westcott GP, Segal AR, Mitri J, Brown FM. Prolonged glucosuria and relapse of diabetic ketoacidosis related to SGLT2-inhibitor therapy. Endocrinol Diabetes Metab. 2020;3:e00117





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