

CASE REPORT

Sodium–glucose cotransporter-2 inhibitors induced euglycemic diabetic ketoacidosis: Two case reports and a review of the literature

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Funding information

No financial Disclosures

Abstract

If not detected early, euglycemic diabetic ketoacidosis can be a serious adverse effect of sodium–glucose cotransporter-2 (SGLT2) inhibitors. Unfortunately, euglycemic diabetic ketoacidosis is underreported in recent trials and missed because of normal blood sugar levels and nonspecific symptoms on presentation. We present two patients with type 2 diabetes mellitus who developed dapagliflozin-associated euglycemic diabetic ketoacidosis followed by hyperglycemic ketoacidosis. The second patient had euglycemic ketoacidosis twice despite instructions to stop using the medication dapagliflozin.

KEYWORDS

dapagliflozin, ketoacidosis, SGLT2 inhibitors

1 | INTRODUCTION

Current treatments for type 2 diabetes have centered on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving insulin sensitivity, delaying the delivery and absorption of carbohydrates from the gastrointestinal tract, or increasing urinary glucose excretion.¹ Sodium–glucose cotransporter-2 (SGLT2) inhibitors reduce blood glucose by increasing urinary glucose excretion.¹ SGLT2 inhibitors are used as second-line therapy in

type 2 diabetes combined with other oral hypoglycemic drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, metformin, sulfonylurea, or basal insulin, in an attempt to achieve good glycemic control, which is based on HbA1c levels.^{1,2}

As a serious complication of DM, diabetic ketoacidosis (DKA) should be recognized early, especially in the face of normal blood sugar levels; otherwise, DKA will become life-threatening. The underlying mechanism of DKA development is a deficiency in insulin activity in the body.³ DKA is frequently seen in individuals with poorly

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controlled type 1 diabetes or those with type 2 diabetes with infections or injuries or in a prolonged fasting. Hyperglycemia is a main feature of DKA, but DKA can occur in the setting of normal blood glucose, especially in patients taking SGLT2 inhibitors.^{3,4} Euglycemic or normoglycemic DKA is defined as DKA that occurs in the presence of a blood glucose concentration of <11 mmol/L (200 mg/dl).³ Euglycemic DKA develops mostly in individuals with type 1 diabetes and rarely occurs in those with type 2 diabetes.³ We present the cases of two patients with euglycemic DKA with no obvious precipitating factor except that they were on SGLT2 inhibitors.

2 | CASE 1

A 64-year-old woman with known diabetes and an oral hypoglycemic agent and glargine basal insulin was recently diagnosed with triple vessel disease and underwent CABG 4 weeks earlier; she was discharged on Glucophage/dapagliflozin, aspirin, and atorvastatin. She visited the emergency department in the cardiac center because of headaches and breathlessness. The patient did not report chest pain, fever, cough, dysuria, or hemoptysis. The patient's blood pressure was 140/70; she was hyperventilating, but her chest sounds were clear. Her blood sugar level was 5 mmol/L. She was reassured that her condition was satisfactory, and she was sent home. Twelve hours later, her level of consciousness deteriorated, and she was brought to the emergency department.

Physical examination showed tachycardia (124 beats/minute), tachypnea (RR 32/minute), low blood pressure (70/40 mmHg), and dry oral mucosa. She was unconscious with shallow breathing, with a Glasgow Coma

Scale score of 7. Emergency physicians successfully intubated her. Her oxygen saturation was 98% on room air. Chest examination was normal, with a clean healed sternal wound, and the remainder of the examination findings were unremarkable. The blood glucose level was 34 mmol/L (normal 4–6.2 mmol/), and kidney function was normal (eGFR 103- estimated by the CKD-EPI). She also had severe metabolic acidosis, with a pH of 6.6 (normal 7.35–7.45), an anion gap of 38 (normal 8–16), and a serum bicarbonate level of 5 mmol/L (normal 22–28) Table 1. Her lactate level was normal, and her hydroxybutyrate level was 9 mmol/L (normal 0.4–0.5 mmol/L). Serum sodium was 143 mmol/L, serum potassium was 5.5 mmol/L, and serum osmolality was 295 mosm/kg. Urine analysis showed no evidence of infection, and urine electrolytes were within normal limits. Urine osmolality was 150 mosm/kg. In the complete blood count, the WBC count was 18,000 cells/mcl. C-reactive protein was within the normal range (5 mg/L). Test results for toxic alcohols, including methanol, ethylene glycol, and diethylene glycol, were negative. There was no osmolar gap. Given her severe anion gap metabolic acidosis and ketoacidosis with a euglycemic–hyperglycemic profile, she was admitted to the ICU and started on infusions of intravenous fluid, insulin (up to 10 units/hour), and dextrose to prevent hypoglycemia (glucose was maintained at approximately 7 mmol/L), and bicarbonate. After a few hours of treatment, laboratory test results showed slow improvement with the dextrose bicarbonate infusion.

Based on the finding of high anion gap metabolic acidosis, with no obvious precipitating factor of ketoacidosis, such as infection or starvation, euglycemic–hyperglycemic ketoacidosis induced by dapagliflozin was considered. Insulin treatment was continued until the ketones were

Admission	Case 1		Case 2	
	Hour 0	Hour 12	Hour 0	Hour 12
Hematocrit, %	33	32	40	38
Sodium, mmol/L	145	144	143	138
Potassium, mmol/L	5.5	4	5.4	
PH	6.6	7.1	6.9	7.2
HCO ₃ , mmol/L	5	10	8.8	
Urea nitrogen, mmol/L	7	4	8	6
Creatinine, μmol/L	90	70	110	80
Lactate, mmol/L	1.2	1	1.4	1.1
Albumin, g/L	34			
Glucose, mmol/L	34	18	6.2	11
Anion gap	38	20		
β-hydroxybutyrate, mmol	9	3.3	6.9	2.4

TABLE 1 Inpatient laboratory values

cleared, and the anion gap was closed in 48 hours while serum glucose levels were maintained. The patient was drowsy and confused the next day, but she improved later and was extubated. CT of the brain was normal. She was discharged on glargine basal insulin, insulin aspart, before meals, and Glucophage. At the 1-month follow-up, the patient was stable, with no neurological deficits and well-controlled blood sugar levels.

3 | CASE 2

The patient, a 56-year-old male, was an ex-smoker who had suffered from diabetes mellitus since 2007. He had no documented retinopathy, nephropathy, or neuropathy. He had been on insulin aspart before each meal, insulin degludec (ultralong-acting basal insulin), and liraglutide (a long-acting glucagon-like peptide-1 agonist) injections. However, 2 months prior to admission, he had been on semaglutide once weekly. His last HBA1C was 8.8.

Three days before admission, the patient did not feel well and was thirsty, losing appetite. On the day of admission, he was weak and got out of bed with the help of his family members but felt dizzy. His son brought him to the ER. He vomited once in the emergency room. He had no fever, chills, rigors, urinary symptoms, headache, skin rash, abdominal pain, or dyspnea. He had not started any new medications, nor did he have a history of illicit drug intake.

His pulse rate was 112 per minute, his respiratory rate was 20/minute, his blood pressure was 120/70 mmHg, and his oxygen saturation was 98% in room air. He also had dry skin.

Laboratory tests (Table 1) showed a pH of 6.99 (normal 7.35–7.45), and HCO₃⁻ of 8.8 mmol/L (normal 22–28), a high anion gap (normal 8–16), a hydroxybutyrate of 6.9 mmol/L (normal 0.4–0.5 mmol/L), and urine ketones +++++. Test results for toxic alcohols, including methanol, ethylene glycol, and diethylene glycol, were negative. There was no osmolar gap. The above picture of normal blood sugar levels and a high anion gap with elevated ketone bodies suggested a diagnosis of euglycemic metabolic acidosis. He was treated with intravenous dextrose fluid with normal saline and insulin infusion in two different intravenous lines, with a bolus of Na₂HCO₃ to keep the pH above 7. The next morning, the anion gap closed, and he felt better. He was provided hydration therapy and was discharged home. His discharge medications were insulin aspart before each meal, insulin degludec, and once-weekly semaglutide.

The patient ran out of acute rapid insulin 3 weeks later and resumed dapagliflozin–metformin 5 mg/1000 mg tablet. Unfortunately, he was readmitted 10 days later with

general fatigue and ketonuria, high blood ketone and blood sugar levels (5 mmol/L), a pH of 7.2, and an HCO₃⁻ of 12 mmol/L. He was managed again with the same protocol and discharged home with extensive counseling to never use this combination of medications again. He was seen 4 weeks later in the diabetic clinic with a fasting blood sugar level of 7 mmol/L and was placed on insulin aspart before each meal and daily insulin degludec.

4 | DISCUSSION

Recently, SGLT2 inhibitors were evaluated in many studies to determine the levels of improvement in renal and cardiovascular outcomes in diabetic and nondiabetic patients. Unfortunately, these studies did not show an increased incidence of DKA compared to placebo. The results of the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS Program Collaborative Group) trial revealed that only a small number of diabetic ketoacidosis events were observed with canagliflozin and placebo (0.6% vs. 0.3% participants with an event per 1000 patient-years; hazard ratio, 2.33; 95% CI, 0.76–7.17).⁵ In the Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure study (EMPEROR-Reduced Trial), there were no reported cases of diabetic ketoacidosis among 1863 patients who received the drug.⁶ In the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial, only 4/2368 (0.2%) participants who received dapagliflozin developed DKA, compared with 4/2368 (0.2%) participants who received placebo.⁷ In the EMPEROR-Preserved Trial, serious adverse events occurred in 1436 patients (47.9%) in the empagliflozin group and 1543 patients (51.6%) in the placebo group. Adverse events led to treatment discontinuation in 571 patients (19.1%) in the empagliflozin group and 551 (18.4%) in the placebo group. DKA was reported in four patients in the empagliflozin group and five in the placebo group. In the SCORED (Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease) trial, DKA occurred in 30 (0.6%) patients in the sotagliflozin group ($N = 5291$) and 14 (0.3%) patients in the placebo group ($N = 5286$; p value 0.02).

All previously mentioned studies falsely reassured cardiologists and nephrologists that DKA incidence does not differ between a treatment drug and a placebo. In March 2015, the US Food and Drug Administration (FDA) issued a warning for SGLT2 inhibitor-associated diabetic ketoacidosis after 20 cases had been reported⁸ (Table 2). In December 2015, the FDA released another statement regarding 73 cases of diabetic ketoacidosis in which the patients required hospitalization or emergency department presentation.⁹ Fifty percent of cases were associated with

TABLE 2 Reported cases of SGLT2 inhibitor induced euglycemic ketoacidosis

Publication	Summary
FDA March 2015 ⁸	March 2013-June 2014 reported 20 cases
FAERS December 2015 ⁹	March 2013-May 2015 reported 73 cases
World Health organization's adverse drug reactions database ¹⁰	487 cases of ketoacidosis exposed to SGLT2 inhibitors, among a total of 68,555 notifications (Adjusted ROR 15.5; 95% CI: 12.8–18.7)
Liu J et al ¹¹	Meta-analysis suggests increased risk of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes compared antidiabetic drugs: 62/34,961 [0.18%] vs. control: 23/25,211 [0.09%]. absolute rate of 3 events per 1000 patient-years

Abbreviations: FAERS, FDA Adverse Event Reporting System; FDA, food and drug administration; ROR, reported odds ratio; SGLT2, sodium–glucose cotransporter-2.

precipitating events, including acute illness (e.g., infection and surgery), reduced oral intake, and reduced insulin dose.⁹ In an analysis of 487 cases of ketoacidosis from the WHO pharmacovigilance database, ketoacidosis was more frequently reported with gliflozins than with other glucose-lowering drugs (adjusted reporting odds ratio 15.5 [95% confidence interval 12.8 to 18.7]).¹⁰ High-quality evidence from a systematic review and meta-analysis (39 RCTs, 60,580 patients) suggested an increased risk of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes compared with placebo or other antidiabetic drugs (relative risk 2.13 [1.38–3.27]), with an absolute rate of 3 events per 1000 patient-years.¹¹

Euglycemic diabetic ketoacidosis occurs in relatively low insulin levels in the face of acute illness or reduced caloric intake. SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, leading to decreased plasma glucose and hence decreased insulin release in the face of an increased counterregulatory response by increased glucagon levels.¹² The decline in circulating insulin levels results in a lowering of the antilipolytic activity of insulin and consequent stimulation of the production of free fatty acids, which are converted to ketone bodies by β -oxidation in the liver.¹² Another possible mechanism of the development of ketosis is that SGLT2 is expressed on the alpha cells of pancreatic islets, and an increase in glucagon serum levels after the administration of dapagliflozin and empagliflozin could explain the ketogenic effects of direct pancreatic stimulation by the drugs.¹³ Important risk factors for precipitating EGDKA are vomiting, dehydration, acute infection, surgery, vigorous or prolonged exercise, and insulin pump or infusion site failure.¹⁴

The first case presented here demonstrates the importance of recognizing the side effects early in view of normal blood sugar levels before DKA becomes a life-threatening condition with severe hyperglycemia and metabolic derangement. The second case confirms the importance of immediately stopping treatment with SGLT2 inhibitors if

diabetic ketoacidosis is suspected or confirmed. Do not restart treatment if another clear precipitating factor for the condition is not identified and resolved as recommended by the European Medicines Agency.¹⁵

In conclusion, following the introduction of the SGLT2 inhibitors in therapeutic practice for type 2 DM treatment and cardiovascular disease, the amount of euglycemic diabetic ketoacidosis increased. DKA caused by SGLT2 inhibitors is a serious complication, and physicians should be aware of early symptoms, check serum and urine ketone levels, and stop the medication before DKA becomes a life-threatening complication. Do not restart SGLT2 inhibitors if clear precipitating factor for the condition is not identified.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The author(s) declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

ZB wrote the article, ZB, OM, and FA shared in the discussion and with WE, KT, Mj, and ME shared in the management and in collecting the data and revision of the manuscript. Our working website is www.kockw.com (Kuwait Oil Company, Ahmadi Hospital).

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Bitar ZI, Maadarani OS, Alabdali F, et al. Sodium–glucose cotransporter-2 inhibitors induced euglycemic diabetic ketoacidosis: Two case reports and a review of the literature. *Clin Case Rep*. 2022;10:e05440. doi:[10.1002/ccr3.5440](https://doi.org/10.1002/ccr3.5440)