Sodium–Glucose Cotransporter 2 Inhibitor–Associated Prolonged Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes: A Case Report and Literature Review

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Background

Sodium–glucose cotransporters (SGLTs) are present in the kidney, gut, and heart. SGLT2 mediates kidney glucose reabsorption predominately through the proximal convoluted tubule. Thus, SGLT2 inhibitors, a novel class of antihyperglycemic medications, enhance glucose excretion in the urine and effectively lower glucose levels in the circulation (1). Because SGLT2 receptors work in a glucose-dependent manner, a higher glycemic load increases the effect of SGLT2 inhibitors and potentiates glucose lowering irrespective of insulin action. Furthermore, due to the high sodium gradient across the membrane of the proximal convoluted tubule, glucose is actively transported with sodium by the SGLT2 receptor into the tubular cells and is later passively reabsorbed (2–4). In addition to their role in diabetes, SGLT2 inhibitors have recently been linked to weight loss and blood pressure reduction, thought to be due to osmotic diuresis (5). More importantly, SGLT2 inhibitors have been shown to improve cardiovascular (CV) physiology and reduce both CV events and all-cause mortality independent of glucose lowering (6–8).

SGLT2 inhibitors increase glucosuria, making the urinary tract a favorable medium for bacterial and fungal growth and, in turn, increasing the incidence of both genitourinary and vaginal yeast infections (9). Hypoglycemia is fairly uncommon with these drugs (4). Drug-drug interactions are rarely reported with SGLT2 inhibitors; therefore, the doses of such medications need not be altered when used with other hypoglycemic agents (4,10). A recent meta-analysis exploring the potential interference of SGLT2 inhibitors with calcium and phosphate concentrations in the blood showed no increase in the risk of bone fracture in patients with type 2 diabetes (11). However, with regard to the adverse events observed with the SGLT2 inhibitors, euglycemic diabetic ketoacidosis (DKA), a serious and life-threatening complication with plasma glucose <200 mg/dL, is probably the most worrisome (12).

Canagliflozin was the first SGLT2 inhibitor approved by the U.S. Food and Drug Administration (FDA), in 2013, followed by dapagliflozin and empagliflozin in 2014. These agents have gained popularity due to their unique mechanism of action, low risk of hypoglycemia, and potential for blood pressure and weight reduction effects (13). In addition, empagliflozin was the first to demonstrate favorable CV outcomes, followed by canagliflozin and dapagliflozin (14–16).

On the other hand, during the first 14 months after SGLT2 inhibitors were approved for use in the United States, 20 cases of DKA were identified through adverse event reporting (17). Reports of the incidence of DKA using data from phase 1–3 randomized controlled clinical trials of SGLT2 inhibitors were subsequently published, with estimated incidences of 0.522 and 0.763 per 1,000 patient-years in patients taking canagliflozin 100 and 300 mg doses, respectively. Additional published data showed a 0.3% incidence of DKA with dapagliflozin compared to an incidence of 0.1% with placebo (16,18,19).

Manufacturers of SGLT2 inhibitors were required to include a risk for DKA in their products' labeling after an FDA issued an alert of the potential DKA associated with these agents in December 2015 (20). Recently, however, the American Association of Clinical Endocrinologists announced that evidence points to a low risk of DKA with

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these medications and concluded that the benefits of use outweigh the risk (21).

Although the mechanism of euglycemic DKA is not entirely elucidated, SGLT2 inhibition decreases plasma glucose levels by 20–25 mg/dL in the fasting and postprandial states (22). This glucose decline decreases insulin production from the β-cells while stimulating α-cells to produce glucagon. Moreover, SGLT2 inhibitors act directly on pancreatic α-cells, thus further increasing plasma glucagon levels, which in turn stimulate hepatic ketogenesis (20). SGLT2 inhibitors may also decrease renal clearance of ketones. These mentioned mechanisms may potentially result in the production of ketone bodies in the presence of normal blood glucose levels and therefore increase the risk for DKA (22).

Case Presentation

Our case is a 57-year-old Caucasian woman with a 5-year history of type 2 diabetes without known complications, hypertension, and asthma, who was admitted to our medical center with right breast tenderness and fever due to a breast abscess, which was worsening despite antibiotic therapy. On admission, she had glucose of 469 mg/dL, bicarbonate of 5 mEq/L, and elevated anion gap of 29 mEq/L consistent with DKA, in the setting of poorly controlled type 2 diabetes, with an elevated A1C of 12.5%. She also had concurrent sepsis from the breast abscess; of note though, her lactic acid level was unremarkable at 1.8 mmol/L (Table 1).

Our patient reported home glucose readings mostly in the 200 mg/dL range, no values >300 mg/dL, and occasional fasting hypoglycemia down to 60 mg/dL. She consumed ~200 g carbohydrate daily, did not exercise, and had been gaining weight steadily; her BMI was between 35 and 40 kg/m^2, indicating class 2 obesity. She had been on glimepiride 4 mg daily and metformin 1,000 mg twice daily, but 3 weeks before admission, glimepiride was discontinued and pioglitazone 30 mg daily and empagliflozin 25 mg daily were added to her metformin. She was taking these three medications until the morning of her admission. She had no known complications from diabetes and reported a significant family history of type 2 diabetes on both paternal and maternal sides.

In the emergency department, she was started on insulin intravenous (IV) infusion per DKA protocol with β-hydroxybutyrate (BHOB) of 7.38 mmol/L, and her glucose decreased to <200 mg/dL within 2 hours. After 12 hours on IV insulin, her bicarbonate increased to 15 mEq/L, the anion gap closed at 10 mEq/L, BHOB decreased to 0.6 mmol/L, and glucose stabilized at 113 mg/dL with normal kidney function (Table 1). Since her anion gap metabolic acidosis (AGMA) was normalized and BHOB was normal, she was appropriately transitioned to a subcutaneous (SC) basal insulin regimen with 25 units of insulin glargine, with

TABLE 1 Laboratory Values Obtained Throughout Hospital Admission

		I&D		I&D			
	Admission T (Last Dose of Empagliflozin)	T + 12 hours	T + 19 hours	T + 48 hours	T + 60 hours	T + 9 days	T + 14 days
Glucose, mg/dL	469→190	113	146	152	163	122	133
Bicarbonate, mEq/L	5	15	7	18	12	26	24
Anion gap, mEq/L	29	10	22	8	17	10	9
BHOB, mmol/L	7.38	0.6	6.45	0.18	2.54	0.3	0.2
Urine ketones	3+	3+	3+	3+	3+	2+	1+
Lactic acid, mmol/L	1.8	1.6	1.3	1.9	1		
Insulin	IV	IV→SC	SC→IV	IV→SC	SC→IV	IV→SC	SC

I&D, incision and drainage; T, time.

discontinuation of the IV insulin drip 2 hours later. The patient was improving on this regimen and was also receiving short-acting insulin lispro with a correction factor of 1 unit for every 50 mg/dL above 150 mg/dL every 4 hours because she was NPO status for further incision and drainage of the breast abscess.

Seven hours later, her bicarbonate level decreased to 7 mEq/L, AGMA increased to 22 mEq/L, and BHOB increased to 6.45 mmol/L. However, the glucose was consistently <150 mg/dL, indicating euglycemic DKA, likely a residual effect of the SGLT2 inhibitor empagliflozin. This circumstance was confirmed with urinalysis showing elevated (3+) glucosuria (Table 1). The patient was restarted on IV insulin per DKA protocol with dextrose-containing fluids to avoid hypoglycemia. Forty-eight hours later, her anion gap closed for three consecutive measurements, glucose was in the mid-100 mg/dL range, BHOB was down to 0.18 mmol/L, and bicarbonate was up to 18 mEq/L (Table 1). At that time, she was again appropriately transitioned to a SC insulin and given insulin glargine 30 units in addition to insulin lispro 10 units three times daily with meals and a lispro correction scale of 1 unit for every 50 mg/dL above 150 mg/dL.

Twelve hours later, while on SC insulin, her bicarbonate level decreased again to 12 mEq/L, AGMA was evident with the gap elevated at 17 mEq/L, glucose was 163 mg/dL, and BHOB was high at 2.54 mmol/L. It was decided once again to resume the IV insulin infusion per DKA protocol. We also monitored her daily urine glucose, which remained persistently elevated at 3+, suggesting a continued effect of empagliflozin as the etiology of euglycemic DKA (Table 1).

The patient continued to be managed on IV insulin infusion for a total of 9 days, with daily monitoring of her urine ketones. On the ninth day, her anion gap had been persistently closed, bicarbonate persistently >20 mEq/L, BHOB was <1 mmol/L, and glucose was within the 110–180 mg/dL range. Urine glucose was 2+ persistently thereafter. On the day of discharge, urine glucose decreased to 1+, but it did not normalize despite 14 days having passed since her last empagliflozin dose (Table 1). At this time, a SC insulin basal-bolus regimen at a 0.7 units/kg total daily dose was initiated, and her glucose was adequately controlled without AGMA. Of note, she had two incision and drainage procedures of her breast abscess, which were performed on the second and fourth days of her hospitalization.

TABLE 2 Description of Various Case Reports With SGLT2 Inhibitor–Associated DKA

Study Characteristics	Karakaya et al. (23)	Yeo et al. (24)	Chou et al. (25)	Sloan et al. (26)	Chakinala et al. (27)
	72-year-old woman with type 2 diabetes	23-year-old woman with type 2 diabetes	61-year-old woman with type 2 diabetes	63-year-old man with type 2 diabetes	61-year-old man with type 2 diabetes
SGLT2 inhibitor	Dapagliflozin	Dapagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Trigger(s)	Surgery	Acute pancreatitis, acute insulinopenia, colitis	Decreased oral intake	Decreased oral intake, myocardial infarction, diverticulitis	Decreased oral intake, insulinopenia
Glucose, mg/dL	136	148	180	239	409
Bicarbonate, mEq/L	9.2	1.8	7	8	14
Anion gap, mEq/L	20.7	23.8	20	Elevated (value not reported)	22
pH	6.9	7.029	6.986	7.15	7.34
BHOB, mmol/L (reference range <0.5)	8	1.6	8	5.2	Not reported
Urine ketones/serum ketones	Positive	2+/2+	Positive	Positive	Positive
Creatinine, mg/dL	1.26	0.81	0.8	0.89	Not reported
Lactate, mmol/L (reference 0.5–1.8)	1.7	1.6	1	Not reported	0.8
Treatment	IV insulin + hydration	Continuous renal replacement therapy	IV insulin + hydration	IV insulin + antibiotics + antiplatelet	IV insulin + hydration

Review of Literature

Multiple case reports of SGLT2 inhibitor–associated DKA have been described in the literature, along with potential triggers (23–27) (Table 2). An Australian case series published in 2018 shed light on the deficiencies associated with such a diagnosis (28) (Table 3).

Our case also complements the others in that surgery, NPO status, infection, and acute illness were likely precipitants. However, our case is unique in that the ketonuria persisted for at least 14 days after the last SGLT2 inhibitor dose. Our patient had resolution of ketonemia as evidenced by BHOB <1 mmol/L twice, but after conversion to SC insulin, she had a sudden increase in BHOB level accompanied by worsening AGMA, which necessitated reverting to IV insulin on both occasions. To our knowledge, there has been no description in the literature of ketonuria of such a duration with SGLT2 inhibitor therapy in conjunction with the need for insulin drip for DKA for a total of 9 days. Notably, this persistent glucosuria is not explained by the terminal elimination half-life (up to 13.1 hours) or by the fraction of empagliflozin excreted in urine and the plasma concentrations within 72 hours (29).

TABLE 3 Summary of a 2018 Australian Case Series by Meyer et al. (28)

Number of cases	13
Hospital course	Nine intensive care unit admissions
Treatment	All IV insulin
SGLT2 inhibitor	Dapagliflozin nine cases; empagliflozin four cases
Diagnosis issues	DKA diagnosis overlooked in two patients, unawareness of the association of SGLT2 inhibitors and DKA in six patients
Triggers	Missed insulin in five cases, undiagnosed type 1 diabetes in two cases, infection in five cases, surgery in three cases, decreased carbohydrate intake in five cases
Conclusion	Most patients did not recognize DKA. Treating physicians did not initially recognize the DKA in many cases due to euglycemia. Treatment was delayed. Most cases were severe and had identifiable triggers.
Recommendations	• Temporary cessation of SGLT2 inhibitors during acute illness and surgery • Caution early on regarding euglycemia associated with DKA • Holding the SGLT2 inhibitor for a period of time after resolution of illness and post-surgery • Ensuring adequate hydration and insulin administration • Delivering an appropriate amount of carbohydrate to avoid ketosis

However, it has been described that increased urinary glucose excretion caused by empagliflozin therapy was maintained for >28 days after multiple dosing of 4 weeks' duration (30).

It is crucial to be able to identify patients presenting with DKA due to SGLT2 inhibitor therapy and to promptly initiate treatment with IV insulin and hydration to prevent sequela. Early recognition and treatment can prevent morbidity, mortality, and prolonged hospital stay. However, more knowledge is needed on the mechanism of the drug's action in promoting the pathogenesis of euglycemic DKA. Additionally, recommendations on the management of this class of drugs perioperatively are warranted.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

A.Y. researched data, wrote the manuscript, edited/reviewed the manuscript, and contributed to discussion. A.S. researched data, edited/reviewed the manuscript, and contributed to discussion. A.Y. is the guarantor of this work and, as such, had full access to all the data in the case presentation and literature review and takes responsibility for the integrity of the information presented.

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