CASE REPORT

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Prolonged ketosis and glycosuria secondary to SGLT2 inhibitor therapy

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Abstract
Clinicians should be aware of the potential for the pharmacologic activity of SGLT2 inhibitors to persist long after the standard drug clearance period of five half-lives, the typical duration used to guide pre-operative medication recommendations.

KEYWORDS
diabetes, euglycemic diabetic ketoacidosis, sodium-glucose cotransporter 2 inhibitors

1 | INTRODUCTION

Current guidelines do not recognize the potential for the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors to persist beyond five half-lives of elimination. The objective of this report is to describe a case of prolonged SGLT2 inhibitor effects and to provide a review of similar cases and outline possible explanatory mechanisms.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as canagliflozin, reduce the reabsorption of filtered glucose at the proximal renal tubules and lower the renal threshold for glucose excretion.[1] This inhibition promotes glycosuria, resulting in decreased plasma glucose and increased risks of volume depletion and mycotic urinary tract infections.[2] SGLT2 inhibitors may also directly act on pancreatic α-cells to increase plasma glucagon levels.[1] These metabolic changes produce a lower insulin-to-glucagon ratio, which can predispose patients to ketoacidosis while maintaining normoglycemia.[1] The objective of this report is to describe a case of SGLT2 inhibitor-associated euglycemic diabetic ketoacidosis (DKA) with prolonged ketosis and glycosuria, and discuss the potential for SGLT2 inhibitor effects to persist well beyond five half-lives of drug elimination.

2 | CASE REPORT

An 81-year-old woman presented to the emergency department (ED) with delirium secondary to dehydration and constipation. She had a past medical history of type 2 diabetes mellitus (T2DM), vascular dementia, stroke in 2017, bioprosthetic aortic valve replacement, multi-vessel coronary bypass surgery, hypertension,

hypercholesterolemia, macular degeneration, and remote cholecystectomy. Medications on presentation are listed in Table 1. Initial investigations in the ED revealed a lactate of 4.7 mmol/L (reference range: 0.5–2.2 mmol/L) and acute kidney injury (AKI) with a creatinine of 95 µmol/L (baseline 50–60 µmol/L; reference range: 50–98 µmol/L). After 1 L of normal saline, there was significant clinical and biochemical improvement (Table 2). Canagliflozin, metformin, and perindopril were all discontinued on presentation.

Two days into her admission, she developed acute respiratory distress with a respiratory rate of 40 breaths per minute and Kussmaul breathing. A venous blood gas revealed a pH of 7.08 (reference range: 7.35–7.45), partial pressure of carbon dioxide of 17 mmHg (reference range: 40–52 mmHg), and a serum bicarbonate of <8 mmol/L (reference range: 23–29 mmol/L). Additional laboratory tests revealed an anion gap metabolic acidosis with marked ketosis and mildly elevated blood glucose (Table 2). She was diagnosed with euglycemic DKA, secondary to recent SGLT2 inhibitor therapy.

We initiated a continuous intravenous infusion of insulin (Humulin R 0.1 units/kg/h). Given euglycemia and low serum potassium, an intravenous infusion of 5% dextrose with potassium chloride (40 mEq/L) was co-administered. Her acid-base status normalized within 24 h, and she was bridged to subcutaneous long-acting insulin with a two hour overlap before discontinuing intravenous insulin. Five hours after stopping the insulin infusion, laboratory investigations demonstrated a recurrent anion gap metabolic acidosis (Table 2). Intravenous insulin was reinstituted and after 24 h of clinical stability, the patient was successfully transitioned to a higher dose of subcutaneous long-acting insulin.

TABLE 1 List of patient medications on presentation to the emergency department

Medication	Dosage
Canagliflozin	100 mg orally daily
Metformin	1 g orally twice daily
Acetylsalicylic acid	81 mg orally daily
Perindopril	4 mg orally daily
Rosuvastatin	10 mg orally daily
Amlodipine	5 mg orally daily
Metoprolol	25 mg orally twice daily
Quetiapine	12.5 mg orally daily
Cyanocobalamin	1000 µg orally daily
Bisacodyl	5 mg orally three times per week
Multivitamin	Orally daily
Cranberry extract	Orally daily

TABLE 2 Laboratory data during course in hospital

	Anion Gap (5–11 mmol/L)	Bicarbonate (23–29 mmol/L)	Lactate (0.5–2.2 mmol/L)	Serum Ketones (mmol/L)	Urine Ketones (mmol/L)	Serum Glucose (3.8–7.7 mmol/L)	Urine Glucose (mmol/L)	Serum Creatinine (50–98 µmol/L)
Day 0: On Presentation	18	21	4.7	–	–	16	–	95
Day 0: After Fluid Resuscitation	14	21	2.0	–	–	7.6	–	62
Day 2: Clinical Deterioration	>24	<5	1.1	8.0	>15.6	11.0	>55	91
Day 3: Insulin Infusion	10	19	–	–	3.9	10.7	>55	64
Day 3: Transition to Long-acting Insulin	16	18	–	–	–	13.0	>55	67
Day 9: After Insulin Dose Reduction	14	19	–	4.0	>15.6	8.5	>55	54
Day 18: After Insulin Cessation	9	22	0.9	Negative	–	6.4	–	44

Note: Reference ranges (where applicable) and units in brackets. Empty cells indicate laboratory tests that were not obtained.

Urine and serum ketone levels remained elevated for another 9 and 10 days (days 13 and 14 of admission), respectively. Urinalysis continued to show significant glycosuria despite euglycemia. An attempt to decrease the dose of long-acting insulin by 25% on day 9 of admission triggered a relapse of ketoacidosis (Table 2). When urine ketones became negative, a more modest reduction in the dose of long-acting insulin by 2 units (12.5%) was tolerated. After three consecutive days of negative serum ketone measurements and a cumulative 16 days of insulin therapy, long-acting insulin was discontinued without issue. The patient was monitored for another 3 days with no recurrence of ketoacidosis, and she was subsequently discharged home with recommendations to discontinue canagliflozin permanently. Outpatient bloodwork 2 months post-discharge showed a serum glucose of 12.1 mmol/L and a normal anion gap.

3 | DISCUSSION

Most cases of SGLT2 inhibitor-associated euglycemic DKA resolve within a few days of treatment.[3] The product monograph of canagliflozin states that the elevation in urinary glucose excretion approaches baseline by approximately 3 days following discontinuation.[2] However, small studies suggest that SGLT2 inhibitor-associated euglycemic DKA may take more than twice as long to resolve as classic DKA.[4] There are several reports of patients who developed euglycemic DKA requiring insulin therapy for 1–2 weeks following SGLT2 inhibitor cessation (Table 3). Classic DKA parameters, such as ketonemia, have been shown to worsen upon insulin dose reductions during euglycemic DKA management, even after normalization of acid-base status (Table 3).

Each SGLT2 inhibitor agent demonstrates distinct pharmacokinetic and pharmacodynamic profiles.[5,6] Compared with other SGLT2 inhibitors, canagliflozin has the highest lipophilicity.[6] Canagliflozin primarily undergoes phase 2 metabolism (which is generally less susceptible to drug-drug interactions) by uridine diphosphate glycosyltransferase enzymes to inactive metabolites.[7] The half-life of canagliflozin is 10.6 h for a 100 mg dose and 13.1 h for a 300 mg dose, with approximately 33% renally cleared.[7] Unbound drug plasma concentrations may not correlate with pharmacodynamic response as evidenced by significant urinary glucose excretion after SGLT2 inhibitor concentrations are diminished in healthy individuals.[5] Although 8 of 13 cases in our literature review on prolonged ketosis and glycosuria secondary to SGLT2 inhibitor therapy were associated with canagliflozin use (Table 3), persistent pharmacologic response may be a class-related adverse event. Sustained urinary glucose excretion response has also been described

among other SGLT2 inhibitors, including dapagliflozin and empagliflozin.[5]

To the best of our knowledge, the etiology of the disconnect between plasma SGLT2 inhibitor concentration and pharmacodynamic response has yet to be fully explained. A case series form Beth Israel Deaconess Medical Center identified 6 patients with type 1 diabetes mellitus or T2DM who developed SGLT2 inhibitor-associated DKA requiring prolonged intensive care unit courses of 4 or more days.[8] These patients were treated with an intravenous insulin infusion for 41.5–132 h, had glycosuria for 3–10 days after SGLT2 inhibitor cessation, and in three cases, experienced relapse of DKA in hospital. The authors postulated that inadequate insulin administration or carbohydrate restriction, concurrent with ongoing SGLT2 inhibitor-induced glycosuria, predisposed patients to DKA relapse.[8] In addition to the above-mentioned case series, we have summarized similar published cases in Table 3.

While insulin is required to treat euglycemic DKA, insulin deficits alone are insufficient to explain the persistence of SGLT2 inhibitor effects—particularly for patients who did not previously require insulin. The exact mechanism of prolonged ketosis and glycosuria far beyond the standard drug clearance period of five half-lives is unknown, but likely contributing factors are detailed in Table 4. In our patient's case, urinary glucose excretion was disproportionately elevated for 14 days after canagliflozin was discontinued. Urinary glucose values may be an imprecise measure of drug activity in patients with renal impairment and our patient presented with an acute kidney injury, which may partially explain the reduced renal excretion of the SGLT2 inhibitor.[7] Medication review also revealed no known drug-drug interactions with canagliflozin.

The American Diabetes Association recommends against the routine in-hospital use of SGLT2 inhibitors and recommends these medications be avoided in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting.[9] Furthermore, the U.S. Food and Drug Administration has advised that SGLT2 inhibitors be stopped at least 3 days before scheduled surgeries (4 days for ertugliflozin) and restarted once risk factors for ketoacidosis are resolved.[9] These guidelines do not acknowledge the potential for the pharmacologic effects of SGLT2 inhibitors to persist for more than the five half-lives of elimination as observed in both surgical and non-surgical settings (Table 3). Furthermore, the delayed presentation and ongoing SGLT2 inhibition 14 days following discontinuation suggests the need for a high level of clinical suspicion for euglycemic DKA throughout the first week of hospitalization, and not only at the time of admission.

TABLE 3 Cases of prolonged euglycemic diabetic ketoacidosis

Reference	Age and gender	SGLT2 inhibitor	Duration of metabolic recovery	Recurrence of euglycemic DKA	Duration of glycosuria	Measurements
Miwa et al.[10]	45-year-old female	Tofogliflozin	60 h	No	5 days	• pH and HCO_3 • Urine glucose
Pujara et al.[11]	50-year-old female	Dapagliflozin	9 days	Yes	9 days	• Serum ketones • Anion gap • Urine glucose
Fukuda et al.[12]	71-year-old female	Canagliflozin	6 days	No	12 days	• Serum ketones • pH and HCO_3 • Urine glucose
Kelmenson et al.[13]	50-year-old woman	Canagliflozin	Unknown	Yes	10 days	• pH • Anion gap • Urine ketones • Urine glucose
Rafey et al.[14]	44-year-old male	Canagliflozin	92 h	No	N/A	• Serum ketones • pH and HCO_3
Rafey et al.[14]	59-year-old female	Empagliflozin	92 h	Yes	N/A	• Serum ketones • pH • Anion gap
Sloan et al.[15]	63-year-old male	Canagliflozin	12 days	Yes	N/A	• Serum ketones • pH and HCO_3
Yehya et al.[16]	57-year-old female	Empagliflozin	9 days	Yes	14 days	• Serum ketones • Anion gap • Urine glucose • Urine ketones
Mistry et al.[17]	47-year-old female	Empagliflozin	5 days	No	N/A	• Serum ketones • pH • Anion gap
Peters et al.[18]	64-year-old female	Canagliflozin	6 days	No	N/A	• Serum ketones • pH • Anion gap
Adachi et al.[19]	27-year-old female	Canagliflozin	4 days	No	5 days	• Venous pH • Urine glucose
Maraka et al.[20]	51-year-old female	Canagliflozin	5 days	Yes	N/A	• Serum ketones • pH • Anion gap
Kohil et al.[21]	65-year-old male	Canagliflozin	8 days	Yes	8 days	• Serum ketones • Anion gap • Urine glucose • Urine ketones

Abbreviations: sodium-glucose cotransporter 2 (SGLT2), diabetic ketoacidosis (DKA), bicarbonate (HCO_3), sodium chloride (NaCl), and uridine diphosphate glucuronosyltransferase (UGT).

Factors contributing to prolonged effect	Intravenous insulin	Subcutaneous insulin	Other therapies
N/A	• 0–60 ; dose increase at 24 h	No	• Dextrose infusion from 12–96 h
• Acute kidney injury • Lack of continuous insulin administration early during hospitalization	• 2 h on day 1 • Restarted on day 6 at 0.8 units/h; increased to 1 unit/h until day 9	• Switched to sliding scale Humalog when blood glucose >10 mmol/L on days 1–5 • Glargine 10 units daily on day 9 and continued for 8 weeks post-discharge	• Dextrose 5% in 0.45% NaCl and 40 mEq KCl at 70 mL/h on days 6–9
• Hypothesized UGT polymorphisms	No	• 2 units of short-acting insulin; increased to 6 units/day	• Continuous renal replacement therapy from days 2–5 • Fluid resuscitation • Dextrose on days 1–2
• Administration of exogenous insulin • Hypothesized UGT polymorphisms	• Drip started after dextrose infusion • Reinstituted after recurrence	• Bridge to glargine and continued for 4 months post-discharge	• 9 L dextrose solution
• Hypothesized transient impairment in β-cell glucose sensing • Hypothesized stimulation of α-cell glucagon secretion	• 1 unit/h and titrated up	• Co-administration of basal insulin • Discharged on glargine 6 units daily and dulaglutide weekly	• Fluid resuscitation
• Acute Kidney Injury • Hypothesized stimulation of α-cell glucagon secretion	• Low dose for initial 28 h • Restarted from hours 44–92	• Aspart 9 units three times daily and glargine 22 units daily after hour 92	• Fluid resuscitation
• Delayed insulin administration	• Alternating fixed (9 units/h) and variable (1–2 units/h) rate infusions for 5 days	• Co-administration of basal insulin • Transitioned to multiple daily injection regime	• Fluid resuscitation
• Incision and drainage procedures on days 2 and 4 of hospitalization	• Initial 12 h • Reinstituted from hours 19–67 • Reinstituted from hour 79 to day 9	• Bridged to glargine 25 units with lispro 1 unit for every 50 mg/dL above 150 mg/dL • Transitioned back to glargine 30 units with lispro 10 units three times daily and lispro correction scale 1 unit for every 50 mg/dL above 150 mg/dL • Basal-bolus regimen at 0.7 units/kg total daily dose at discharge	• Dextrose solution
N/A	• Drip for 5 days	• Discharged on glargine and lispro	• Dextrose drip for 5 days
• Hypovolemia • Hypothesized hyperglucagonemia	• Drip for 6 days	No	• Dextrose drip for 6 days
• Administration of exogenous insulin • Increase in glomerular filtration rate • Hypothesized delayed reversibility of SGLT2 inhibition	• Infusion for 3 days	• Switched to multiple daily injections	• Isotonic saline for 1 h switched to 5% dextrose
• Solitary kidney and acute kidney injury • Hypothesized hyperglucagonemia	Yes	• Transitioned to glargine 10 units daily and aspart correction as needed (6 units/day)	• Intravenous fluids
• Hypothesized continued drug binding to renal transport proteins	• Initiated on postoperative day 4 • Restarted on postoperative day 9	• Switched on postoperative day 8 • Transitioned back on postoperative day 11 and discharged on a subcutaneous insulin regimen	• Sodium bicarbonate ampules and infusion • Dextrose-containing fluids

TABLE 4 Factors potentially contributing to prolonged SGLT2 inhibitor effect

Potential Factors	Effect
Slow off-rate of SGLT2 inhibition	• Prolonged urinary glucose excretion despite low canagliflozin plasma concentrations[5]
Metabolizing enzyme polymorphisms	• Increased systemic exposure to canagliflozin in patients with genetic polymorphisms in the UGT1A9 and UGT2B4 enzymes[22]
Decreased renal function	• Increased systemic exposure to canagliflozin[7] • Slightly lengthens the half-life of the drug[7] • Age-associated loss of renal function predisposes to kidney injury, which extend beyond changes in glomerular filtration rate[23]
Drug lipophilicity	• Increased adiposity in older adults expands the volume of distribution[6] • Potential increase in the elimination half-life of canagliflozin[6]

4 | CONCLUSION

As the indications for SGLT2 inhibitor therapy expand, the underlying mechanisms of prolonged ketosis and glycosuria merit further study. Possible explanatory factors include a slow off-rate of SGLT2 inhibition, metabolizing enzyme polymorphisms, decreased renal function, and drug lipophilicity. More practically, inpatient physicians should be aware of the possibility of a prolonged period of insulin dependency in admitted patients who develop euglycemic DKA related to SGLT2 inhibitor use. Furthermore, clinicians should also be aware of the potential for drug effects to persist well beyond five half-lives, the typical period used to guide pre-operative medication recommendations.

CONFLICT OF INTEREST
No conflicts of interest.

AUTHOR CONTRIBUTIONS
DB, RK, PW, and LLS contributed to the conception and design of the manuscript. DB, RK, and LLS wrote the initial draft of the manuscript. DB, PW, and LLS edited the draft and reshaped it into this manuscript. All authors approved final version of manuscript and agree to be responsible for all aspects of the work.

ETHICAL APPROVAL
This report did not necessitate formal review and approval from an institutional review board or ethics committee.

CONSENT
The authors have obtained informed consent from the patient for publication.

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