Severe Prolonged SGLT2i-induced Euglycaemic Diabetic Ketoacidosis Refractory to standard Therapy and Dialysis: Case report and literature review

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Abstract

Sodium Glucose Cotransporter Type 2 Inhibitors (SGLT2i) are oral hypoglycaemic agents that have insulin-independent glucose-lowering mechanism mediated by increasing renal excretion of glucose through inhibition of SGLT2-mediated renal glucose reabsorption. Euglycaemic diabetic ketoacidosis (eDKA) induced by SGLT2i is increasingly recognized side effect. Here, we describe a 26 years old male patient with Type 2 diabetes mellitus (T2DM) and morbid obesity. He was on multiple oral hypoglycaemic agents including SGLT2i. He developed life-threatening severe prolonged eDKA associated with SGLT2i (Canagliflozin) precipitated by adenovirus infection. The acidosis was not responding to standard DKA therapy and renal replacement therapy and was managed effectively with insulin titration based on capillary ketone measurements. We reviewed the literatures for the

reported cases of severe prolonged eDKA induced by SGLT2 inhibitors and treatment modalities used.

Keywords: Sodium Glucose Cotransporter Type 2 (SGLT2i) Inhibitors, Canagliflozin, Euglycaemic Diabetic Ketoacidosis, Severe metabolic acidosis, Haemodialysis

Introduction

Sodium Glucose Cotransporter Type 2 Inhibitors (SGLT2i) are not known only for its glycaemic and weight reduction effects, but has a cardiovascular (CV) disease risk reduction in T2DM patients as well as renal protective effects in patients with chronic kidney disease. However, there are emergent safety issues with SGLT2i use including eDKA, bone fractures, acute renal injury, fournier's gangrene and lower limbs amputations (1).

In clinical trials with SGLT-2 inhibitors, eDKA rates ranged between 0.2 to 0.8 cases per 1,000 patient-years among T2DM patients (2). It is characterized by normal or near normal glucose levels (<250 mg/dl, (13.9 mmol/L)), which may delay recognition and management of the condition (1). Precipitants of DKA include surgery, extensive exercise, myocardial infarction, stroke, severe infections, prolonged fasting, and other stressful physical and medical conditions (2). Here, we describe a 26 year old male patient with poorly controlled T2DM on multiple oral hypoglycaemic agents, who developed life-threatening severe eDKA associated with SGLT2 inhibitor use (canagliflozin). The acidosis was prolonged and refractory to standard DKA therapy and renal replacement therapy and was managed effectively with insulin titration based on capillary ketone measurements.

Case Report

A 26 year old male presented to our hospital's emergency department early January 2020 with four hours history of agitation, shortness of breath and abdominal pain. This was preceded by four days history of fatigue, malaise, fever and sore throat. He recently joined the national military service. He was diagnosed with T2DM for seven years and was following in another institute and maintained on multiple oral hypoglycaemic agents of which he could recall only metformin by name. He reported no history of recent travel. Physical examination was remarkable for dry oral mucosa. He was in distress, febrile 38.5^{o} c, tachycardic 110 beats per minute, tachypniac 28 breaths per minute and had blood pressure of 110/50 mmHg after 2 litters of normal saline given in the military campus. He is morbidly obese with BMI of 41.52 kg/m2 (Weight 120 Kg, Height 170 cm). He had non-exudative pharyngitis. Chest exam revealed shallow deep breathing and bilateral vesicular breathing without added sounds. Cardiac exam was normal apart from sinus tachycardia. There was mild epigastric tenderness and other systemic examination was unremarkable.

Initial investigations revealed mild hyperglycemia (13.6 mmol/L), severe metabolic acidosis with bicarbonate level of 4 (22-29) mmol/L and venous blood pH was 6.84 (7.35-7.45). He had high anion gap of 34. Urine ketones were 15 mmol/L (3+) and lactic acid level was normal 2 (0.5-2.2) mmol/L. He had leukocytosis with white blood count of 29 (4.5-11) x10^{9}/L, hemoglobin of 16.4 (13.2-17.3) g/l and platelet count of 350 (140-400) x10^{9}/L. His c-reactive protein (CPR) was elevated 64 (≤5) g/L as well as procalcitonin 2.3 (≤0.5) ng/ml. The toxicology screen for alcohol and illicit drugs was negative. He had normal sodium 135 (135-145) mmol/L, potassium levels 3.8 (3.2-5.5) mmol/L, creatinine 85 (62-106) micrommol/L and urea level 4 (2.8-8.1) mmol/L. He had no rhabdomyolysis with normal total creatinine kinase of 223 (39-308) IU/L. The serum osmolality was elevated 315 (275-295) mOsm/kg. Liver function test and thyroid test were normal.

Based on the above, broad-spectrum antibiotic was started and diabetic ketoacidosis protocol was initiated with 10 units of insulin bolus followed by insulin infusion. With another five litters of crystalloid fluid, his pH remained the same. Therefore, Sodium bicarbonate (HCO_3) infusion was administered intermittently (initial total of 250 mls of 8.4% $NaHCO_3$); nonetheless pH remains static around 6.99 (Fig 1). Nephrology was consulted for renal replacement therapy. Within few hours from presentation he developed respiratory distress and required assisted ventilation.

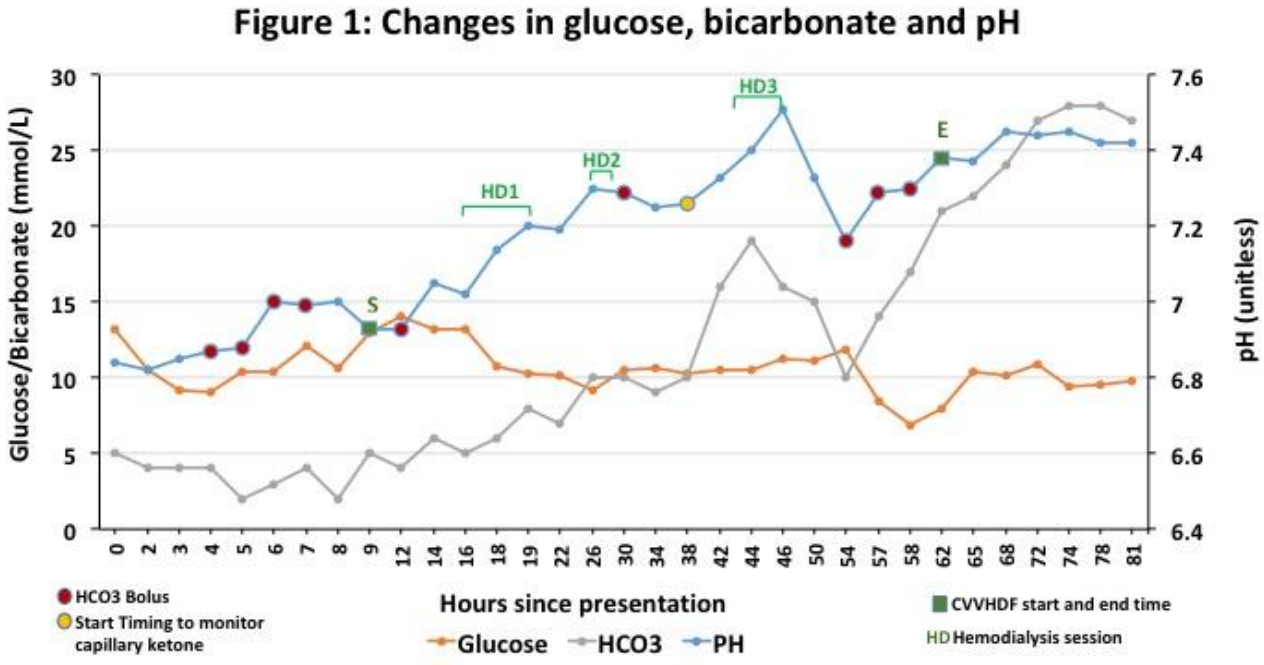

Figure 1: Changes in glucose, bicarbonate and pH since presentation and timings of renal replacement therapy.

Point of care inpatient ketone measurement was not available in our hospital and the insulin rate was titrated based on serial glucose measurements which was well controlled with insulin infusion at a rate of 1 unit/hr. Basal insulin was started from second day of admission along with insulin infusion.

After 18 hours from presentation, family were able to bring his home medications, which included daily gliclazide 120 mg, canagliflozin 300 mg, pioglitazone 30 mg, liraglutide1.8 mg injection and metformin/sitagliptin (1000/50 mg) twice daily. It was reported that he had uncontrolled diabetes and refused to start insulin as per his primary physician's recommendations. Later, we could clarify that he was on canagliflozin 300 mg daily for the last three years.

Thirty eight hours after presentation, serial capillary blood ketone measurements using the FreeStyleOptium ketone meter (Precision Xceed!; Abbott Diabetes Care, Maidenhead, UK) was initiated to titrate insulin infusion rate along with escalation of both dextrose and Intravenous potassium (KCL) replacement aiming for ketosis clearance (Fig 2). He received a total of three sessions of intermittent haemodialysis (3 hours each) and continuous veno-venous hemodiafiltration (CVVHDF) with dose of 30 mL/kg/hr starting before first dialysis session and continued in between and after the last dialysis session (Fig 1). In between he required further HCO_3 boluses as well (Fig 1). It took sixty-two hours to correct metabolic acidosis, to close anion gap with renal replacement therapy and titration of insulin rate based on capillary ketones.

Figure 2: Changes in glucose, capillary 3-hydroxybutyrate and insulin infusion rate

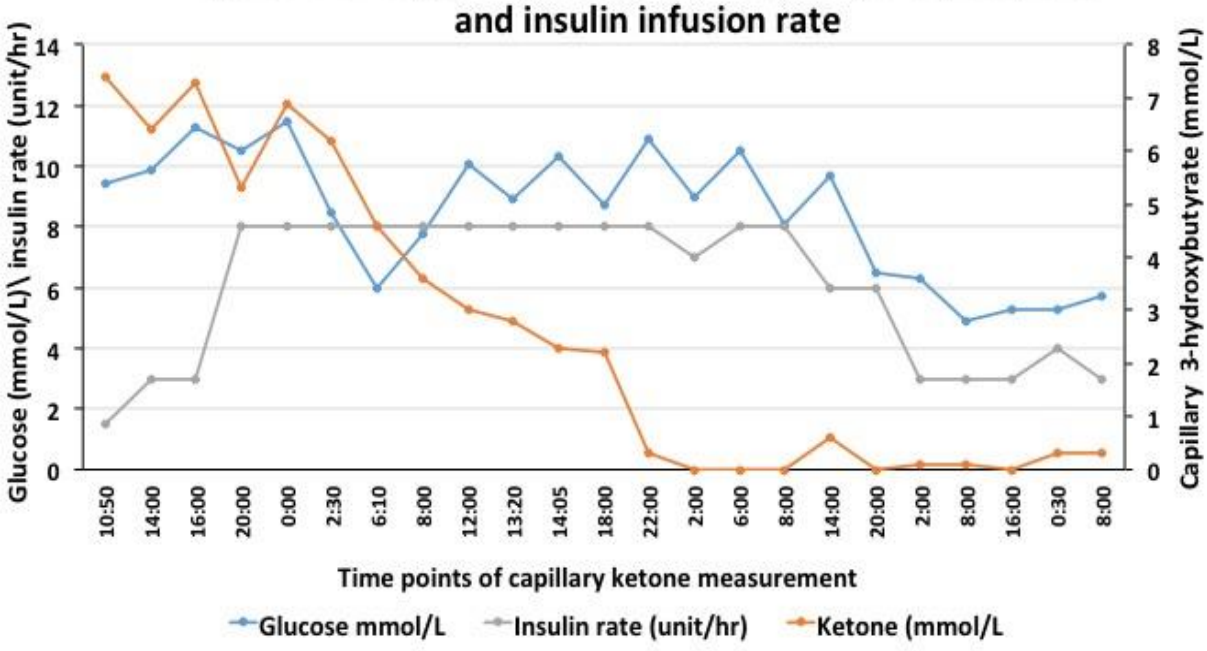

Figure 2: Insulin infusion rate and changes in capillary ketones measurement.

He was extubated on day 4 and shifted to basal bolus regimen on day 5 of hospitalization. Despite resolution of DKA, ketonemia (>0.6 mmol/L) was persistent till day 12 of hospitalization. Prior to knowing his home medications, and in view of the refractory nature of the severe metabolic acidosis, metabolic team was consulted to rule out possibility of inborn errors of metabolism. Urine organic acid profile revealed peaks of 2-ketoisovaleric acid, acetoacetic acid, 3-OH butyric acid and 2-OH isovaleric acid suggestive of ketosis and advanced catabolism. In addition to that, he was noticed to have significant diuresis on the first twenty-four hours of presentation (Figure 3).

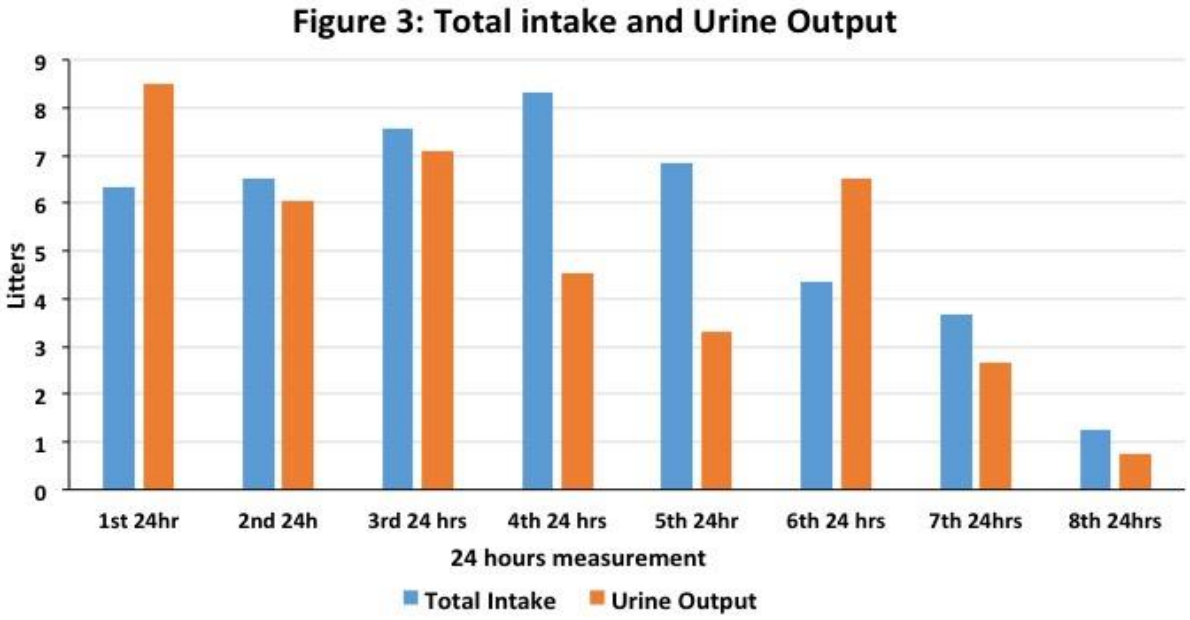

Figure 3: Total fluid intake and output.

Further investigations including blood, sputum and urine cultures were negative. Influenza screen, Strep A, HIV, hepatitis B and C were also negative. Respiratory viral panel MDX was positive for adenovirus. Chest X ray was normal initially. His HbA1C was 13.3%, C-peptide 0.11 nmol/L (0.37-1.47), Anti IA2, GAD antibodies and insulin antibodies were negative.

His hospital course was complicated with provoked femoral line site deep venous thrombosis and pulmonary embolism that was managed with anticoagulation. His total admission hospital course was sixteen days.

Discussion

SGLT2i are a class of oral glucose-lowering agents that were introduced to the market in 2013. The increased risk of euglycemic diabetic ketoacidosis (DKA) was detected on the post-marketing setting leading the U.S. Food and Drug Administration (FDA) in 2015 to issue a drug safety communication that warns of an increased risk of eDKA associated with the use of all approved sodium–glucose cotransporter 2 inhibitors (3).The FDA also identified potential triggering factors such as intercurrent illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake.

A study using a large claims database in the USA found that the incidence of DKA within 180 days following initiation of SGLT2i was 2.2-folds higher than with dipeptidyl peptidase-4 inhibitors (DPP4is), the latter of which have no known association with DKA (4). From reports to the US Food and Drug Administration Adverse Event Reporting System (FAERS), Fadini et al (2017) calculated proportional reporting ratios (PRR) of 7.9 (95%CI 7.5- 8.4) for DKA in reports including vs those not including an SGLT2i and having a diabetes indication and was higher for type 1 diabetes (5).

In cardiovascular outcome trials (CVOTs), the proportion of patients with reported diabetic ketoacidosis was similar in the SGLT2 inhibitor and placebo groups for empaliflozin (EMPA-REG OUTCOME) and canagliflozin (CANVAS program), but it was higher for dapagliflozin (DECALRE-TIMI 58) with HR of 2.18 (95% CI 1.10, 4.30; P = 0.02) (1).

Limenta et al (2019) provided demographic and baseline laboratory investigation profiles of 20 DKA cases associated with SGLT2i that had been reported to the Health Sciences

Authority (HSA), Singapore. Apart from the difference in blood glucose levels, there were no noted differences in the profile between typical and euglycaemic DKA cases. However, no data were provided regarding duration of DKA resolution and ICU stay (6).

A recent Korean study compared DKA characteristics between patients treated with and without SGLT2i reported that patients using SGLT2i needed longer ICU stays compared to non-users (4 days vs 2 days, P=0.019). It showed as well that on average DKA episodes developed after 124 days (range: 7-380 days) of starting SGLT2 inhibitors (7).

Several retrospective cohort of non-SLGT2i DKA reported average time to biochemical resolution of DKA of 11-12 hrs (8). The longer duration of SLGT2i associated DKA is not emphasised in current management guidelines and has not been widely described in the literature. One reason could be that the majority of reported cases were managed successfully with standard DKA protocol and there has been no much focus or recognition on DKA resolution duration in this specific group.

On the other hand, the impact of morbid obesity on DKA outcomes have been highlighted on few retrospective studies. Elsheikh et al (2018) reported increased mortality associated with morbid obesity in patients with DKA (adjusted odds ratio 1.37 (95% CI, 1.18-1.61), while a body mass index of (30-40) was not associated with increased mortality (9). Similarly, Mudgal et al (2019) performed nation wide analysis and found that DKA patients who were morbidly obese had increased mortality compared to those without morbid obesity (0.72% vs. 0.38%, adjusted odds ratio 1.85, p=0.04). In addition, the study reported that obese DKA patients had a longer length of stay (3.79 vs. 3.14 days, p<0.001) compared to their non-obese counterparts (10). It is worth mentioning that in the Korean study, there was no difference in the body mass index between SGLT2i users vs nonusers (7).

Subsequent published case reports have made important contributions to the knowledge about characteristics of this serious adverse effect. In Table 1, we summarized some of reported

cases characteristics with our current case. Like other cases, insulin rate during infusion is higher and the duration is prolonged. Therefore, insulin infusion titration rate should be based on serum ketone measurements rather than serum glucose in order to clear ketones faster. Following closely the serum levels of ketone and adjusting insulin infusion rate is crucial to prevent recurrence of ketoacidosis in the recovery phase.

Renal replacement therapy (RRT) was required in our patient like in other few reported cases (Table 1). Whether the titration of insulin infusion rate from the start of DKA protocol based on serum ketones rather than glucose will correct the acidosis faster and hold the need for RRT is something worth to be looked for in future cases. However, in previous reported cases, despite that the insulin rate was as high as 10 units/hr, RRT was still needed. The underlying pathophysiologic process of SGLT2 inhibitor associated ketoacidosis could explain this. In addition to its effect in reducing pancreatic insulin secretion, increase glucagon secretion by direct stimulation of alpha pancreatic cells, increase conversion of fatty acids to ketone bodies by beta-oxidation in the liver (lipolysis), SGLT2 inhibitor can increase ketone and acetoacetate reabsorption in renal tubules and decrease renal ketone excretion (17).

Table 1: Reported cases of severe prolonged eDKA with SGLT2i use and modalities of treatment.

Case	**Diabetes Type + Other medications**	**SGLT2 Inhibitor**	**Precipitating**	**BMI** (kg/m2)	**Glucose**	**Bicarbonate (mmol/L)**	**Anion gap (mEq/L)**	**Ketone (mmol/L)**	**PH**	**Treatment**	**Comment**	**Duration of metabolic acidosis**
Current report	26 y/o M T2DM FOR 7 years+ multiple OHAs (poorly controlled)	Canagliflozin 300mg	Infection	41.5	13.6 mmol/L	4	34	Urine Ketone 3+ (15mmol/)	6.84	Insulin infusion+ NaHCO3+ 3Hemodialysis sessions+ CVVHDF	Intubation+ Ketonemia persisted for total 12 days	62 hrs.
Sloan G et al. 2018 (11)	63 y/o M T2DM for 23 years + On Mixed insulin	Canagliflozin 7 months before presentation	Silent myocardial infarction and diverticulitis.	27.2	13.3 mmol/L	8	--	5.2	7.15	Fixed and Variable insulin infusion rates	Ketonemia persisted for total 12 days	5 days of IV insulin
Maadarani O et al. 2016 (12)	44 y/o M T2DM for 8 years + Insulin glargine and glimepiride	Dapagliflzin 5 mg one month before presentation	No identifiable factor	31	142 mg/dl	6	35	10	7.006	Insulin infusion up to 10units/hr + NaHCO3 + 8hrs CVVH	.	48 hrs.
Gelaye A et al. 2016 (13)	54 y/o M T1DM + insulin glargine	Canagliflozin 300mg 3 years before presentation	Postoperative Day 2 Laparoscopic appendectomy	--	142 mg/dl	9	37	12.4	7.058	Insulin infusion up to 10 units/hr+ NaHCO3 infusion+ Hemodialysis	Intubation +Fomepizole	72 hrs.
Rafey M et al. 2019 (14)	44 y/o M T2DM for 5 years+ GLP-1 agonist (Poorly controlled)	Canagliflozin 300mg	Postop Day 6 post C5-C7 cervical decompression	38.8	9.4 mmol/L	44.8	33.8	4.3	7.1	Insulin infusion +basal insulin		92 hrs.
Rafey M et al. 2019 (14)	59 y/o F T2DM for 17 years+ basal bolus insulin (Poorly controlled)	Empagliflozin 25 mg 5 months before	Postop Day 3 elective laparoscopic right partial nephrectomy	39	12.3 mmol/L	9.3	32	4.8	7.23	Insulin infusion	Stopping DKA protocol after 28 hrs after normalization of Glucose and Ph lead to relapse	92 hrs.
Nappi F et al. 2019 (15)	67 y/o F T2DM for 5 years + metformin	Empaglilozin 25mg 1 month before presentation with Low calories intake	NA	21.5	299 mg/dl	1.8	31	After 12hrs urine ketone 80 mg/dl	6.91	Insulin infusion+ NaHCO3+ 2 days hemodialysis		1 week
Yeo S et al.2018 (16)	23 y/o F T2DM + metformin	Dapagliflozocin 10 mg 2 years	Hypertriglyceridemia induced pancreatitis	--	148 mg/dl	1.8	NA	Urine ketones 2+	7.029	Conservative DKA management+ CRRT for 2 days		NA

Conclusion

With the expanding list of indications and use of SLG2i, it is worth to be aware of the special characteristics of DKA associated with it and the need of higher insulin infusion rate to clear ketosis.

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