Periprocedural Euglycemic Diabetic Ketoacidosis Associated With Sodium–Glucose Cotransporter 2 Inhibitor Therapy During Colonoscopy

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More than 10% of adults undergoing colonoscopy have type 2 diabetes (T2D) (1). The use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has increased due to their glycemic control and benefits of lowering cardiovascular morbidity and mortality as well as reducing diabetic nephropathy (2,3).

Diabetic ketoacidosis (DKA) is a rare complication associated with SGLT2i. Precipitating factors include fasting, dietary modifications, intercurrent illnesses, surgical stress, insulin insufficiency, and inappropriate management of SGLT2i in the periprocedural period. SGLT2i-induced ketoacidosis can present either with elevated blood glucose levels (BGL) or with near-normal BGL (<250 mg/dL), termed euglycemic diabetic ketoacidosis (EDKA) (4). Interventional gastroenterology procedures, in particular colonoscopy, pose risk for EDKA with SGLT2i use due to cathartic bowel preparation, fluid-only dietary restriction, and fasting. We present a series of cases of EDKA in the setting of colonoscopy and discuss its procedure-specific implications.

Eight cases of SGLT2i-associated EDKA in the setting of colonoscopy were identified between August 2019 and February 2020 across three centers. Five cases were identified through the Central Adelaide Local Health Network (CALHN), South Australia, and three were identified at the Royal Brisbane and Women's Hospital (RBWH), Queensland. Ethical approval was obtained from the CALHN (13194) and RBWH (LNR/2020/QRBW/61873) Human Research Ethics Committees.

All patients had T2D and were aged between 45 and 75 years (Table 1). One patient was on a very-low-calorie diet, which may have been a contributory factor. Duration of T2D ranged from 18 months to 20 years, and HbA_{1c} ranged from 36 to 87 mmol/mol (5.4% to 10.1%). All patients were prescribed metformin and a variety of other diabetes drugs, including insulin (two patients). The SGLT2i prescribed were dapagliflozin ($n = 4$) and empagliflozin ($n = 5$). Seven patients took SGLT2i up to the day prior and one took it on the morning of colonoscopy.

Patients presented with a spectrum from mild (case 1) to severe ketoacidosis (cases 6 and 8). Interestingly, two patients were asymptomatic (cases 7 and 8). Acidosis varied with a pH range 7.18–7.33, bicarbonate 12–21.7 mEq/L, and serum ketones 2–5.2 mmol/L. All patients fulfilled criteria for EDKA. Seven patients were identified preprocedure, three proceeded with their colonoscopy, and colonoscopy was rescheduled for four. EDKA was noted after the procedure in one. All patients received treatment; intravenous (i.v.) insulin/dextrose ($n = 5$), subcutaneous (s.c.) insulin ($n = 2$), and oral carbohydrate intake ($n = 8$). Treatment took place across the wards ($n = 6$), postanesthesia care unit ($n = 1$), and emergency department ($n = 1$). All patients recovered, and SGLT2i therapy was recommenced in four.

This is the first case series of SGLT2i-associated EDKA occurring in patients undergoing colonoscopy and has implications for periprocedural management. While our case series is small, it highlights a number of key points. Despite variability in duration of T2D, age, glycemic control, and other diabetes therapy, there is a risk of EDKA if SGLT2i are not held. All but one held their SGLT2i on the morning of the procedure. As euglycemia is a feature of SGLT2i-associated EDKA, BGL is not a diagnostic criterion. In contrast to reports in other settings, colonoscopy patients were systemically well (4). Patients

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Table 1—Eight cases of SGLT2i-associated DKA in the setting of colonoscopy

Case	1	2	3	4	5	6	7	8
Sex	Male	Male	Female	Male	Male	Female	Male	Female
Age, years	53	75	69	60	60	45	55	79
Type of diabetes	T2D	T2D	T2D	T2D	T2D	T2D	T2D	T2D
Type 1 autoantibodies	N/A	Anti-GAD, anti-IA2, and islet cell antibodies negative	N/A	N/A	N/A	Anti-GAD and anti-IA2 antibodies negative (but two previous episodes of DKA)	N/A	N/A
HbA_{1c}, mmol/mol (%)	60 (7.6)	53 (7.0)	87 (10.1)	69 (8.5)	36 (5.4)	66 (8.2)	50 (6.7)	64 (8.0)
Duration of diabetes	2 years	13 years	20 years	18 months	N/A	19 years	5 years	4 years
SGLT2i	Dapagliflozin 10 mg	Empagliflozin 25 mg	Dapagliflozin 10 mg	Empagliflozin 25 mg	Empagliflozin 5 mg BD	Dapagliflozin 5 mg OD	Empagliflozin 12.5 mg OD	Empagliflozin 12.5 mg BD
OHA	Metformin 1 g TDS, linagliptin 2.5 mg BD, arcabose 100 mg TDS	Metformin 1 g OD, glipzide 2.5 mg	Metformin 1 g TDS	Metformin 1 g BD, sitagliptin 100 mg, gliclazide MR 60 mg OD	Metformin 1 g BD	Metformin XR 1 g OD	Metformin XR 1 g OD	Metformin XR 1 g BD, pioglitazone 30 mg OD
Insulin	None	None	NovoMix 30/70 25 IU breakfast, 12 IU dinner	None	None	Lantus 30 IU nocte, Humalog variable dose 4 IU per 15 g carbohydrate (~40 IU per day)	None	None
SGLT2i withheld prior to procedure	Y: morning of procedure	Y: morning of procedure	Y: morning of procedure	Y: morning of procedure	Y: morning of procedure	Y: morning of procedure (took evening prior)	N: took morning of procedure	Y: morning of procedure
Bowel preparation	4 L of Glycoprep-C	4 L of Glycoprep-C	Low-fiber diet 4 days, Magnesia San Pellegrino BD 4 days, 4 L of Glycoprep-C	4 L of Glycoprep-C	Clear fluids from lunch day prior, 3 L of colonLYTELY	Low-fiber diet 5 days, magnesium citrate, bisacodyl, 3 L of Glycoprep-C	Low-fiber diet 5 days, magnesium citrate, bisacodyl, 3 L of Glycoprep-C	Low-fiber diet 5 days, magnesium citrate, bisacodyl, 3 L of Glycoprep-C
Onset of DKA	Prior to procedure	Prior to procedure	Prior to procedure	Prior to procedure	Post procedure	Prior to procedure (before 3rd L of Glycoprep-C)	Prior to procedure	Prior to procedure
BGL, mg/dL (mmol/L)	154.8 (8.6)	79.2 (4.4)	237.6 (13.2)	158.4 (8.8)	136.8 (7.6)	93.6 (5.2)	91.8 (5.1)	154.8 (8.6)
pH	7.29	7.18	7.24	N/A	N/A	7.33	7.30	7.25
Ketones, mmol/L	2	2.9	4.2	2.8	3.1	3.1	4.7	5.2
Anion gap, mmol/L	23	22	23.1	N/A	27	13	18	22

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Table 1—Continued

Case	1	2	3	4	5	6	7	8
Bicarbonate, mEq/L	21.6	21.7	16.8	N/A	17	12	17	14
Base excess, mmol/L	−5.1	−5.9	−9.4	N/A	N/A	−11.9	−8.0	−12.0
Procedure delayed?	N	Y (by 4 weeks)	Y (by 4 weeks)	N	N	Y (by 5 days)	N	Y (by 1 day)
Management	i.v. insulin and dextrose; oral intake	i.v. insulin and dextrose, followed by Lantus 10 units s.c.	i.v. insulin and dextrose; oral intake	Oral intake and s.c. insulin	Oral intake only	Oral intake and s.c. insulin	i.v. insulin and dextrose; oral intake.	i.v. insulin and dextrose; oral intake
Location	Ward	Ward	Ward	Postanesthesia care unit	Ward	Emergency department	Ward	Ward
Insulin infusion duration	26 h	11 h	18 h	4.5 h	N/A	Discharged home after 2 h of monitoring	12 h	22 h
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered
SGLT2i recommenced	Y (3 days later)	N	Unknown	Y (1 day later)	N	Y (6 weeks later)	N	Y (4 days later)

BD, twice a day; IU, international units, dependency unit; N, no; N/A, not available; OAH, oral antihyperglycemic; OD, once daily; TDS, three times a day; Y = yes.

presenting for colonoscopy have many of the same precipitating factors (e.g., very-low-calorie diet, volume depletion, reduced insulin administration/secretion) as those observed in bariatric surgery patients (5). It appears that bowel preparation increases EDKA risk, while the colonoscopy procedure itself may not. All but one case occurred prior to colonoscopy; three patients proceeded to colonoscopy without worsening of their EDKA. Notably, EDKA has not been observed with upper endoscopy. EDKA risk may be related to fluid and electrolyte shifts associated with bowel cleansing with an osmotic laxative, the effect of which may be potentiated by an SGLT2i acting on the sodium–glucose cotransporter 1 on the apical membrane of enterocytes. Furthermore, a period of "low-residue diet" preceding bowel preparation may lead to a longer relative fasting period.

SGLT2i-associated EDKA in the setting of colonoscopy presented along a spectrum of clinical severity varying from mild ketosis without significant acidosis to severe ketoacidosis and was asymptomatic in two. Acid-base status must be assessed in all patients with elevated ketones even if they are well, to differentiate ketoacidosis from the more common and less harmful ketosis without acidosis.

This case series shows that EDKA can occur in patients undergoing bowel preparation who cease their SGLT2i on the day of colonoscopy. At a minimum, SGLT2i should be stopped 2 days prior to colonoscopy to allow washout of the SGLT2i to start before bowel preparation. In complex, high-risk patients, a conservative approach would require ceasing SGLT2i prior to the low-residue diet. It is prudent to encourage adequate hydration and caloric intake (e.g., glucose-containing clear fluid) during catharsis to limit fluid and electrolyte shifts. Ensuring patients are scheduled first on a procedural list may avoid excessive fasting. Even when this approach is adopted at an institutional level, occasionally this advice will not be followed by patients. A strategy is needed for patients who present for colonoscopy who have taken an SGLT2i during this preprocedural period or those who present with symptoms suggestive of EDKA. We recommend that a finger-prick ketone threshold exceeding 1.0 mmol/L should prompt the need for a blood gas to look for metabolic acidosis. Patients with a base excess of less than −5 confirming ketosis with acidosis warrant treatment with an i.v. insulin/dextrose infusion. Deferral of nonurgent colonoscopy is the safest approach; however, our case series suggests it may be possible to safely proceed with colonoscopy in selected milder cases (e.g., base excess greater than −10), provided treatment with i.v. insulin/dextrose is administered. Those without acidosis (base excess greater than −5) warrant endocrinology advice but mostly could proceed with colonoscopy.

A caveat to withholding SGLT2i medication is inducing hyperglycemia, with the risk even greater if the SGLT2i is prescribed in pill combination. An alternate strategy would be to continue the SGLT2i until the day of bowel preparation as long as patients were able to monitor finger-prick ketone levels.

As the patient cohort taking SGLT2i and undergoing colonoscopy is likely to grow, more research is required to determine incidence, define those "at risk," identify the optimal time to stop SGLT2i, and determine the safety of proceeding with colonoscopy in patients with mild-to-moderate EDKA.

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