ACS Case Reviews in Surgery
Vol. 4, No. 2

Euglycemic Diabetic Ketoacidosis After Robotic-Assisted RYGB in a Patient Taking an SLGT-2 Inhibitor: A Re-Examination of Guidelines

AUTHORS:
Johnson KR; Kuhn JE; Daouadi M

CORRESPONDING AUTHOR:
Kelly R. Johnson, DO
New York Breast Health
805 Northern Boulevard
Great Neck, NY 11021
Email: kelly.r.johnson9@gmail.com

AUTHOR AFFILIATION:
Geisinger Medical Center, Danville, PA 17822

Background	SGLT-2 inhibitors are a newer class of medications used to treat diabetes mellitus type 2. However, these drugs have raised some concerns regarding perioperative management, as they have been found to cause the rare adverse event of euglycemic ketoacidosis, which may be life-threatening and difficult to diagnose because blood glucose levels often remain within range.
Summary	A 37-year-old morbidly obese female presented for elective bariatric gastric bypass surgery with a BMI of 43.6. The contributing comorbidities related to her obesity include diabetes mellitus type 2, hypercholesteremia, hypertension, and obstructive sleep apnea requiring CPAP. Her diabetic medication regimen included empagliflozin 25 mg orally daily, metformin 1,000 mg orally twice daily, and regular insulin of 50 units with lunch and 60 with dinner. The patient underwent an uneventful robotic-assisted laparoscopic Roux-en-Y gastric bypass, liver biopsy, and upper endoscopy. On postoperative day (POD) 1, her labs demonstrated an anion gap of 27 with a bicarbonate level of 6; the patient became tachycardic at 110–120 beats/min and tachypneic up to 28 breaths/minute, and her blood glucose (BG) was noted to have increased to 181–198 mg/dL. Due to her profound acidosis and worsening clinical picture, the patient was transferred to the ICU for further workup and closer monitoring. Urinalysis was obtained, which demonstrated ketones >160 and glucose >1,000. It was determined that her acidosis was likely secondary to diabetic ketoacidosis (DKA), but her acidosis was out of proportion to her blood glucose levels. Her chart was reviewed, and it was noted that she had been on empagliflozin preoperatively, which is known to cause euglycemic DKA. She was kept in the ICU and treated with insulin infusion, dextrose, and a bicarbonate infusion. On POD 6, she was discharged home.
Conclusion	We advocate for revising the current guidelines regarding the perioperative management of SGLT-2 inhibitors. Due to the prolonged half-life, we advise stopping these medications at least three days or 72 hours prior to major surgery. We recommend closely monitoring blood glucose levels and insulin requirements for bariatric patients on a low-carbohydrate or high-protein diet within two weeks of surgery. These levels can drastically change during this time, predisposing patients to euglycemic diabetic ketoacidosis (euDKA). We urge surgeons, endocrinologists, and anesthesiologists to be mindful of the preoperative hyperglycemic agents their patients are prescribed and to be able to recognize the precipitating risk factors as well as the signs and symptoms of euDKA.

Key Words	diabetes; SLGT-2 inhibitors; bariatric surgery; diabetic ketoacidosis

DISCLOSURE STATEMENT:
The authors have no conflicts of interest to disclose.

FUNDING/SUPPORT:
The authors have no relevant financial relationships or in-kind support to disclose.

MEETING PRESENTATION:
Keystone Chapter American College of Surgeons Scientific Meeting, 2019

RECEIVED: December 15, 2020
REVISION RECEIVED: October 28, 2020
ACCEPTED FOR PUBLICATION: November 24, 2020

To Cite: Johnson KR, Kuhn JE, Daouadi M. Euglycemic Diabetic Ketoacidosis after Robotic-Assisted RYGB in a Patient Taking an SLGT-2 Inhibitor: A Re-Examination of Guidelines. *ACS Case Reviews in Surgery*. 2023;4(2):41-44.

Case Description

A 37-year-old morbidly obese female presented for elective bariatric gastric bypass surgery with a BMI of 43.6. The contributing comorbidities related to her obesity include diabetes mellitus type 2, hypercholesteremia, hypertension, and obstructive sleep apnea requiring CPAP. Her preoperative hemoglobin A1C was 5.9, and her diabetic medication regimen included empagliflozin 25 mg oral daily, metformin 1000 mg orally twice daily, and regular insulin 50 units with lunch and 60 with dinner. For 14 days preoperatively, she was maintained on a high-protein liquid diet. It was discussed with the patient preoperatively that her insulin requirements would decrease while on the high-protein liquid diet. She did not require any insulin correction during these two weeks. She was instructed to stop her lisinopril 48 hours prior to surgery and metformin and empagliflozin 24 hours before surgery. On the morning of surgery, her preoperative blood glucose (BG) was 129 mg/dL.

The patient underwent an uneventful robotic-assisted laparoscopic Roux-en-Y gastric bypass, liver biopsy, and upper endoscopy. Throughout the surgery, she remained hemodynamically stable, and her blood glucose levels exceeded 150 mg/dL; therefore, she was started on an insulin infusion intraoperatively per Geisinger protocol.

Immediately postop, her pain was controlled, she was tolerating a stage 1 bariatric diet by POD 0 without nausea or vomiting, her vitals were stable, and she was independently ambulating. She was seen by our bariatric medicine specialist postop, who did not anticipate having to restart any of her oral diabetic medications and noted that her insulin requirements would likely decrease.

On POD 0, her blood glucose ranged from 132–164 mg/dL. She required 0–1 unit of insulin/hour (u/hr) POD 0–1. In the early morning of POD 1, she was feeling well overall but complained of shortness of breath on exertion. She was advanced to a stage 2 bariatric diet, and her insulin infusion was discontinued.

Her POD 1 morning lab results demonstrated a leukocytosis of 26.6, potassium of 5.3, and she was found to have a profoundly acidotic anion gap of 27 with a bicarbonate level of 6. Repeat labs were ordered for the afternoon, and a chest X ray and arterial blood gas (ABG) were obtained stat (Table 1). Chest X ray was unremarkable. Later that morning, the patient became tachycardic at 110–120 beats/min and tachypneic up to 28 breaths/minute, and her BG was noted to have increased to 181–198 mg/dL. The insulin infusion was restarted with requirements ranging from 9 to 16 u/hr. A CT scan of the abdomen and pelvis was ordered that showed normal postoperative changes and no evidence of a leak or an obstruction.

Due to her profound acidosis and worsening clinical picture, the patient was transferred to the ICU for further workup and closer monitoring. Urinalysis was obtained, which demonstrated ketones >160 and glucose >1000. It was determined that her acidosis was likely secondary to diabetic ketoacidosis (DKA), but her acidosis was out of proportion to her blood glucose levels. Her chart was reviewed, and it was noted that she had been on empagliflozin preoperatively, which is known to cause euglycemic DKA, and the diagnosis was made. The patient was kept in the ICU and treated with insulin infusion, dextrose, and a bicarbonate infusion. She was also started on Zosyn empirically out of concern for possible intraabdominal infection due to leukocytosis. She was monitored closely with q1h accuchecks, q4h BMP, and serial blood gases. Her blood gases can be seen in Table 1.

Table 1. Postop AB

	POD 1	POD 1	POD 1	POD 2	POD 5
pH (7.35-7.45 u)	7.070	7.030	7.117	7.323	7.354
FiO2 (%)	21	–	–	–	21
PCO2 (35-45 mm Hg)	<17.0	<17.0	<17.0	29.7	26.5
PO2 (75-100 mm Hg)	122.0	121.0	119	110	94.1
Bicarbonate (23-31 mmol/L)	–	–	–	15	14.4
Base deficit (0-2 mmol/L)	–	–	–	9.5	9.5

Fraction of inspired oxygen (FiO2)
Partial pressure of carbon dioxide (PCO2)
Partial pressure of oxygen (PO2)

On POD 2, her tachycardia improved to 90–106 beats/min, and her respiratory rate improved by 17–24 breaths/min, remaining on room air and CPAP at night. Her insulin requirements decreased from 5 u/hr to 1 u/hr. Her anion gap closed, electrolytes replaced and monitored, started on a stage 1 diet, and she was transitioned off dextrose and started on Plasma-Lyte maintenance fluid.

On POD 3, her anion gap opened again, her blood glucose levels were low, and she was restarted on dextrose. The insulin drip was titrated to 1–2 u/hr, her vital signs were stable, and she was advanced to a stage 2 diet. Zosyn was discontinued as cultures were negative. She was deemed stable for transfer to the med-surg floor.

From POD 4 to 6, the patient's vital signs remained stable, and the insulin infusion was titrated off. She was transitioned to an insulin sliding scale, and her blood glucose levels remained within normal range. She was followed by bariatric medicine, endocrinology, and the diabetes educator during her stay. She was discharged on POD 6 to home and instructed to stop metformin and empagliflozin and continue Lantus 25 units daily and 1:15 carb coverage with sliding scale insulin with meals.

Discussion

SGLT-2 inhibitors are among the newest medications for managing diabetes mellitus type 2 (T2DM). This drug binds to sodium-glucose cotransporter-2 (SGLT2) receptors found in the proximal convoluted tubule. It inhibits glucose reabsorption, causing glycosuria and the excretion of glucose and sodium in the urine.[1-3] This drug is very effective in promoting glycemic control without an increased risk of hypoglycemia, has renal and cardiovascular benefits and promotes weight loss, and comes in an oral formulation.[1] Nevertheless, during the perioperative period, this drug has been increasingly reported to cause the life-threatening adverse effect of euDKA.[4-8]

SGLT-2 inhibitors have a rapid onset with a time-to-peak (TTP) of 1-2 hours and a long half-life of 10.6-16.6 hours.[1] Empagliflozin specifically has a TTP of 1.5 hours and a half-life of 12.5 hours.[1] The current perioperative guidelines recommend that SGLT-2 inhibitors be stopped 24 hours before surgery. The half-life of these medications extends past this 24-hour window and has been shown to have serious adverse effects in the perioperative period.

During the perioperative period, the human body experiences increased metabolic demand, stress, dehydration, and limited oral intake, which can contribute to a ketogenic state.[1] SGLT-2 inhibitors contribute to this ketogenic state by increasing renal absorption of ketones and enhancing ketogenesis, which can lead to worsening ketoacidosis.[1] Over the last few years, there has been an increasing number of case reports of euDKA associated with SGLT-2 inhibitors in post-surgical patients and, even more specifically, bariatric patients.[4-8]

Euglycemia DKA is a rare condition. It differs from DKA because blood glucose levels do not usually exceed 250 mg/dl.[2] Common symptoms of euDKA include abdominal pain, tachypnea, altered mental status, nausea and vomiting, and respiratory failure requiring intubation. Workup will reveal an anion gap metabolic acidosis and elevated plasma ketone levels. The diagnosis is challenging because blood glucose levels do not exceed 250 mg/dL, so it is essential for medical providers to be aware of this disease process and has a high index of suspicion when their patient is known to be on an SGLT-2 inhibitor preoperatively.[1]

It is recommended by the American Association of Clinical Endocrinologists and the American College of Endocrinology that SGLT-2 inhibitors be stopped a minimum of 24 hours prior to elective surgery and three days prior to major surgery.[1-3] At Geisinger, we now recommend stopping SGLT-2 inhibitors 72 hours before surgery after this case. The elimination half-life of these medications is, on average, 13.6 hours; therefore, the effects may last up to 3-4 days.[2,3] Patients who undergo diet modifications, fasting, and/or who are dehydrated are at an increased risk of developing DKA and may need to be off these medications for a longer period before surgery.[1,2] Bariatric patients are maintained on a high protein, low carbohydrate diet for two weeks before surgery, which can pre-dispose them to euDKA. Milder et al. recommended that SGLT-2 inhibitors be stopped two weeks before surgical intervention.[3] Additionally, this population experiences rapid weight loss postoperatively, nausea, emesis, and dehydration, increasing the risk of developing ketoacidosis.[3] Prevention is the key, so it is important to know which of our bariatric patients are on SGLT-2 inhibitors to ensure they stop these medications at the appropriate time before surgery. It has also been suggested to check preoperative plasma and urinary ketones to recognize those pre-disposed to developing DKA.[3]

Conclusion

The use of SGLT-2 inhibitors in diabetic type 2 and reports of euDKA in surgical patients requiring extensive workup and ICU admission before the diagnosis are on the rise. We advocate for revising the current guidelines regarding the perioperative management of SGLT-2 inhibitors. Due to the prolonged half-life, we advise stopping these medications at least three days or 72 hours before major surgery. We recommend closely monitoring blood glucose levels and insulin requirements within two weeks of surgery for bariatric patients on a low-carbohydrate or high-protein diet. These levels can drastically change during this time, pre-disposing patients to euDKA. We urge surgeons, endocrinologists, and anesthesiologists to be mindful of the preoperative hyperglycemic agents their patients are prescribed and to be able to recognize the precipitating risk factors as well as the signs and symptoms of euDKA.

Update: As of March 20, 2020, the FDA has revised labels for SGLT-2 inhibitors, recommending that these medications be stopped at least 3-4 days prior to scheduled surgery due to the risk of developing ketoacidosis.[9]

Lessons Learned

euDKA is a life-threatening and difficult-to-diagnose complication known to be associated with SGLT-2 inhibitors. This case demonstrated the importance of reducing the risk for euDKA in our bariatric (and likely all surgical patients) by discontinuing SGLT-2 inhibitors 72 hours prior to elective surgery.

References

1. Bardia A, Wai M, Fontes ML. Sodium-glucose cotransporter-2 inhibitors: an overview and perioperative implications. *Curr Opin Anaesthesiol*. 2019;32(1):80-85. doi:10.1097/ACO.0000000000000674
2. Brown F, McColl T. Euglycemic Diabetic Ketoacidosis Secondary to Dapagliflozin Use: A Case Report. *J Emerg Med*. 2018;54(1):109-111. doi:10.1016/j.jemermed.2017.10.001
3. Burke KR, Schumacher CA, Harpe SE. SGLT2 Inhibitors: A Systematic Review of Diabetic Ketoacidosis and Related Risk Factors in the Primary Literature. *Pharmacotherapy*. 2017;37(2):187-194. doi:10.1002/phar.1881
4. Hoenes C, Rashid Q, Pimentel J. Diabetic ketoacidosis in a postoperative gastric bypass patient. *J Surg Case Rep*. 2017;2017(7):rjx148. Published 2017 Jul 28. doi:10.1093/jscr/rjx148
5. Lane S, Paskar D, Hamed S, Goffi A. When Guidelines Fail: Euglycemic Diabetic Ketoacidosis After Bariatric Surgery in a Patient Taking a Sodium-Glucose Cotransporter-2 Inhibitor: A Case Report. *A A Pract*. 2018;11(2):46-48. doi:10.1213/XAA.0000000000000734
6. Milder DA, Milder TY, Kam PCA. Sodium-glucose co-transporter type-2 inhibitors: pharmacology and peri-operative considerations. *Anaesthesia*. 2018;73(8):1008-1018. doi:10.1111/anae.14251
7. Pace DJ, Dukleska K, Phillips S, Gleason V, Yeo CJ. Euglycemic Diabetic Ketoacidosis Due to Sodium-Glucose Cotransporter 2 Inhibitor Use in Two Patients Undergoing Pancreatectomy. *J Pancreat Cancer*. 2018;4(1):95-99. Published 2018 Nov 15. doi:10.1089/pancan.2018.0016
8. van Niekerk C, Wallace J, Takata M, Yu R. Euglycaemic diabetic ketoacidosis in bariatric surgery patients with type 2 diabetes taking canagliflozin. *BMJ Case Rep*. 2018;2018:bcr2017221527. Published 2018 Aug 20. doi:10.1136/bcr-2017-221527
9. FDA Drug Safety Communication. FDA revises labels of SGLT2 inhibitors for diabetes to include . U.S. Food and Drug Administration. www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious. Published March 19, 2020. Accessed February 26, 2021.