

Novel cause of postoperative anion gap acidosis in a patient with diabetes following gastrectomy

Huda A Muhammad ,¹ Raja R Narayan ,¹ Marina Basina,² George A Poultsides¹

¹Section of Surgical Oncology, Department of Surgery, Stanford University School of Medicine, Stanford, California, USA

²Division of Endocrinology, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

Correspondence to

Dr George A Poultsides; georgep1@stanford.edu

SURGICAL DILEMMA

A woman in her 60s with non-insulin-dependent diabetes was found to have a CDH1 mutation from genetic workup after colectomy for sigmoid colon cancer discovered on diagnostic colonoscopy for rectal bleeding 6 years earlier. She pursued annual endoscopic surveillance until several foci of intramucosal, poorly differentiated, signet ring adenocarcinoma were found a month prior to her operation. Notably, her glucose levels were normal on outpatient checks, but her last hemoglobin A1c within the 3 months leading up to her operation was 7.4%. Her diabetes had been managed with sitagliptin-metformin 50 mg to 1000 mg two times per day, glipizide 15 mg daily, and empagliflozin 25 mg daily. She underwent an uncomplicated total gastrectomy, D2 lymphadenectomy, and Roux-en-Y esophagojejunostomy reconstruction. She progressed well postoperatively. She had no leak on an esophagogram performed with water-soluble contrast on postoperative day 2. By postoperative day 3, she was passing gas, had weaned to only oral pain medications, and advanced to her intended discharge diet of full liquids. Her diabetic medications had been held and an insulin sliding scale had been ordered with fewer than 4 units needed daily. Her point-of-care glucose levels ranged from 79 mg/dL to 201 mg/dL during this time.

Despite meeting these discharge criteria by postoperative day 3, her bicarbonate declined from 26 mmol/L preoperatively to 9 mmol/L, with a widening anion gap from 14 preoperatively to 23. She otherwise remained afebrile, hemodynamically stable, and asymptomatic without nausea, vomiting, diarrhea, or tachypnea. She felt fatigue, thirst, and had high-volume urine output of 5.7L during the last day despite weaned intravenous fluids. Her abdominal examination was as expected, with minimal tenderness and no distension. Her lactate level returned to normal at 0.9 mmol/L and creatinine remained normal at 0.42 mg/dL.

WHAT WOULD YOU DO?

- Discharge the patient home.
- Consult nephrology to aid in the workup of her anion gap acidosis.
- Trend her bicarbonate and anion gap during the next 24 to 48 hours.
- Order CT of the abdomen and pelvis with intravenous contrast to rule out infection.

WHAT WE DID AND WHY

- Consult nephrology to aid in the workup of her anion gap acidosis.

The nephrology service was consulted and requested a urinalysis, discovering 3+ glucose and 2+ ketones. The patient had no prior episodes of diabetic ketoacidosis (DKA). With no history of renal failure, starvation, or alcoholism, the patient was diagnosed with euglycemic DKA from empagliflozin use, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor. This, combined with starvation, stress from surgery, and altered nutrient absorption, contributed to euglycemic DKA.

Her ketoacidosis was corrected by resuscitation with 5% dextrose and normal saline at 125 mL/hour, starting an insulin drip between 0.7 and 1 unit/hour, with a glucose goal of 120 mg/dL to 160 mg/dL, and potassium replenishment. She transitioned off the insulin drip on postoperative day 5 after her anion gap closed. Since the empagliflozin had contributed to euglycemic DKA, the endocrinology service was consulted to re-evaluate her outpatient diabetic regimen. She was recommended to continue sitagliptin-metformin, stop empagliflozin, and start using 6 units of glargine. She was discharged home on postoperative day 6. She unfortunately developed shortness of breath and palpitations 3 days later, prompting her to present to the emergency department where her glucose was 196 mg/dL, her anion gap was 18, and her urinary ketones were 1+ and glucose 3+. She was admitted for euglycemic DKA and discharged home 48 hours later on 16 units of glargine nightly and metformin 500 mg two times per day.

Her course illustrates the need for surgeons to understand the complications of common antihyperglycemic medications and their pharmacokinetics. There are eight classes of oral medications that mediate glycemic homeostasis (table 1).

Metformin suppresses liver gluconeogenesis and is the first-line treatment for type 2 diabetes. SGLT-2 inhibitors block glucose reabsorption from renal proximal tubules. In a randomized trial comparing SGLT-2 inhibitors with placebo, experimental arm patients had lower risk of cardiovascular and renal complications. If a second agent is needed beyond metformin, an SGLT-2 inhibitor should be considered especially for patients at high risk of cardiovascular disease or diabetic nephropathy. The combination of metformin+SGLT-2 inhibitors reduces hemoglobin A1c and controls systolic blood pressure better than other combinations, thus SGLT-2 inhibitor use has increased. Unfortunately, as noted in this case, SGLT-2 inhibitors can lead to euglycemic DKA through carbohydrate depletion while inhibiting glucose reabsorption in the kidneys due to its long half-life (~12 hours) during early

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Table 1 Classes of oral antihyperglycemic medications for patients with type 2 diabetes

Class	Medication	Mechanism	Effect on body weight	Benefit	Adverse effect
Biguanide	▶ Metformin.	Inhibits hepatic glucose production.	Mild weight loss.	Reduces MI by 39% and coronary deaths by 50%.	Lactic acidosis.
Sulfonylurea	▶ Glyburide. ▶ Glipizide. ▶ Glimperiride.	Increases insulin secretion.	Weight gain.	Very capable of lowering serum glucose.	High risk of hypoglycemia and increased cardiovascular disease risk.
Meglitinide	▶ Repaglinide. ▶ Nateglinide.	Glucose-dependent increase in insulin secretion.	Weight gain.	Very capable of lowering serum glucose, with less risk of hypoglycemia as sulfonylurea.	Risk of hypoglycemia effected by inhibitors of CYP3A4 or CYP2C8 in the liver.
Thiazolidinediones	▶ Rosiglitazone. ▶ Pioglitazone.	Insulin sensitizer.	Weight gain.	Minimal risk of hypoglycemia.	Heart failure, pioglitazone associated with bladder cancer, and fractures.
Alpha-glucosidase inhibitors	▶ Acarbose. ▶ Miglitol. ▶ Voglibose.	Decrease metabolism and absorption of intestinal polysaccharides.	Mild weight loss.	Mild decrease in hemoglobin A1c.	Flatulence, abdominal discomfort, and diarrhea, and transaminitis.
Dipeptidyl peptidase-4 inhibitors	▶ Alogliptin. ▶ Linagliptin. ▶ Sitagliptin. ▶ Saxagliptin. ▶ Vildagliptin.	Inhibit degradation of glucagon-like peptide.	Neutral.	Decrease postprandial triglycerides.	Pancreatitis and upper respiratory tract infection.
Sodium-glucose cotransporter-2 inhibitors	▶ Canagliflozin. ▶ Dapagliflozin. ▶ Empagliflozin. ▶ Ertugliflozin.	Glucosuria due to blocking (90%) of glucose reabsorption in renal PCT; insulin-independent mechanism of action.	Weight loss.	Reduce sodium and uric acid absorption, reduce systolic blood pressure, and reduce renal failure progression.	Euglycemic ketoacidosis, fractures, and genital mycosis.
Glucagon-like peptide 1 (GLP-1) receptor agonists	▶ Semaglutide. ▶ Liraglutide. ▶ Exenatide. ▶ Dulaglutide.	Activate GLP-1 receptor, increased insulin and decreased glucagon secretion, delayed gastric emptying, and increased satiety.	Weight loss.	Cardiovascular risk reduction.	Nausea, vomiting, pancreatitis, and C cell tumor of the thyroid (contraindicated in MEN type 2).

CYP, cytochrome P450; MEN, multiple endocrine neoplasm; MI, myocardial infarction; PCT, proximal convoluted tubules.

postoperative diet restriction. This contributes to an overall insulin-deficient state instigating lipolysis and ketoacidosis. During this period of limited oral intake, intravenous carbohydrate supplementation should be considered.

Awareness of complications from common antihyperglycemic medications is essential in the management of surgical patients. Especially in the perioperative period when substantial changes to the antihyperglycemic regimen occur in the setting of diet restriction and the physiological response to an operation (especially a total gastrectomy where nutrient absorption is additionally impaired), consideration of preoperative medications should inform interpretation of postoperative patient progression.

Twitter Raja R Narayan @rajarnarayan and George A Poultides @poultides

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ORCID iDs

Huda A Muhammad <http://orcid.org/0000-0001-6521-0402>
Raja R Narayan <http://orcid.org/0000-0001-7938-4702>