Euglycemic diabetic ketoacidosis associated with the use of a sodium–glucose cotransporter-2 inhibitor

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A 70-year-old man with long-standing type 2 diabetes mellitus, paroxysmal atrial fibrillation and dyslipidemia presented to the emergency department with nausea, vomiting and generalized weakness. The patient had been on his current antidiabetes regimen for a few years, which included metformin, liraglutide, modified release gliclazide and empagliflozin. His most recent glycated hemoglobin (HbA1c) level was 7.8%, and he had no history of diabetic ketoacidosis. The patient had been discharged from hospital a few days earlier after having undergone coronary artery bypass surgery with no complications. He had been receiving insulin subcutaneously perioperatively while the antidiabetic agents he usually took were held one day preoperatively. Upon discharge, he resumed taking his usual medications.

On initial evaluation in the emergency department, the patient was found to have left lower lobe pneumonia. Laboratory investigations showed a pH of 7.27 (normal 7.36–7.44), a bicarbonate level of 10 (normal 22–31) mmol/L, an anion gap of 31 (normal 7–15) mmol/L, a near-normal glucose level of 11.2 (normal 3.9–11.0) mmol/L and an elevated white blood cell count of 22 (normal 4–11) $\times 10^9$ cells/L. The β-hydroxybutyric acid level was elevated, at more than 3.2 (normal < 0.3) mmol/L, but venous lactate was within the normal range. Urinalysis showed the presence of ketones. The patient was given fluids intravenously, insulin perfusion and antibiotics (ceftriaxone, intravenously). The anion gap decreased to 20 within five hours of therapy starting, and the patient was transitioned to insulin given subcutaneously. Within 48 hours, the anion gap had normalized, the insulin regimen was discontinued, and the patient was restarted on metformin, liraglutide and modified release gliclazide; the empagliflozin, however, was not restarted.

Discussion

Diabetic ketoacidosis (DKA) is a complication commonly associated with type 1 diabetes mellitus, but may also occur with type 2 diabetes in states of relative insulin deficiency. Since the approval of sodium–glucose cotransporter-2 (SGLT-2) inhibitors for the treatment of type 2 diabetes by the United States Food and Drug Administration (FDA) in March 2013, an increasing number of cases of ketoacidosis has been described. This increase led the FDA to issue a warning in May 2015 regarding the risk of ketoacidosis in patients with type 2 diabetes who are taking an SGLT-2 inhibitor (canagliflozin, dapagliflozin and empagliflozin).[1] Near-normal glycemic values were reported in many of these cases, which potentially delayed the recognition and treatment of the ketoacidosis.

In a recently published cohort study with a 1:1 propensity matching of patients with type 2 diabetes who had received a new prescription of an SGLT-2 inhibitor compared with patients who received a new prescription for a dipeptidyl peptidase-4 (DPP-4) inhibitor, the risk of hospital admission for diabetic ketoacidosis was reported to be higher with the SGLT-2 inhibitors.[2] Indeed, the rate of hospital admission for diabetic ketoacidosis was significantly higher with SGLT-2 inhibitors compared with DPP-4 inhibitors (4.9 v. 2.3 events per 1000 person-years).[2] After propensity-score matching, the hazard ratio was 2.2 (95% confidence interval 1.4–3.6). The absolute risk of hospital admission for diabetic ketoacidosis with SGLT-2 inhibitors was about 1% and was apparent within 30 days of starting the medication. [2]

KEY POINTS

- Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have been associated with euglycemic diabetic ketoacidosis.
- Precipitants to ketoacidosis include intercurrent illnesses, surgery, decreased carbohydrate intake, dehydration and excessive alcohol intake.
- Patients taking SGLT-2 inhibitors should receive counselling about diabetic ketoacidosis; if patients feel unwell, their urine or serum should be evaluated for the presence of ketones.
- If ketones are present, SGLT-2 inhibitors should be withheld, hydration should be maintained and insulin therapy should be considered.

The diagnostic criteria for diabetic ketoacidosis includes arterial pH of 7.3 or lower, serum bicarbonate of 15 mmol/L or less, anion gap greater than 12 mmol/L and the presence of ketones in the urine or serum.[3] Euglycemic diabetic ketoacidosis has been empirically defined as a blood glucose level of less than 14 mmol/L and a plasma bicarbonate level of 10 mEq/L or lower.[4] Diabetic ketoacidosis occurs as a consequence of insulin deficiency with an increase in counter-regulatory hormones. This hormonal imbalance increases hepatic glucose production and decreases peripheral glucose uptake, which leads to hyperglycemia, glucosuria, osmotic diuresis and dehydration. In addition, insulin deficiency and glucagon excess increase the mobilization of fatty acids from white adipose tissue and their transportation to the liver. As a result, the capacity of hepatocyte mitochondria to metabolize fatty acids via the Krebs's cycle is overwhelmed, which leads to the production of ketone bodies by alternate ketogenic pathways.[5] The elevation of serum ketones thus results in high anion gap metabolic acidosis.[6]

Sodium–glucose cotransporter-2 is a protein located in the brush border of epithelial cells in the proximal convoluted tubule, which reabsorbs 90% of filtered glucose. Inhibitors of this protein block that reabsorption, causing glucosuria. The increased urinary glucose excretion creates an osmotic diuresis and net caloric loss, which leads to reductions in blood pressure and body weight.[7]

Although the mechanism that leads to the atypical presentation of diabetic ketoacidosis in patients who receive SGLT-2 inhibitors is not fully understood, plausible explanations exist.[5] Sodium–glucose cotransporter-2 inhibitors lower blood glucose levels, thus reducing insulin secretion from pancreatic β-cells, and might directly enhance the release of glucagon from α cells. The combination of increased glucagon levels and decreased insulin levels results in increased lipolysis and ketogenesis.[8] In addition, SGLT-2 inhibitors may augment the renal tubular reabsorption of ketone bodies by inhibiting sodium reabsorption.[9]

A systematic review of case reports identified three main precipitating factors for diabetic ketoacidosis in patients taking SGLT-2 inhibitors: latent autoimmune diabetes in adults (36%), surgery (28%) and stopping or reducing insulin (28%).[10] In addition, the FDA also issued a list of risk factors that may precipitate diabetic ketoacidosis in patients with type 2 diabetes taking SGLT-2 inhibitors (www.fda.gov/Drugs/DrugSafety/ucm475463.htm). These factors include increased insulin requirement (intercurrent illnesses and surgery), insulin deficiency, severe dehydration, decreased carbohydrate intake and excessive alcohol consumption.

Patients should receive counselling about the risk factors for euglycemic diabetic ketoacidosis and should be informed about its symptoms, including nausea, vomiting, abdominal pain, hyperventilation, confusion and fatigue. The Canadian Diabetes Association recommends that patients who are feeling unwell undergo evaluation for the presence of ketones in their serum or urine, even when blood glucose levels are relatively normal.[3] Serum ketones may be preferred over urine ketones because β-hydroxybutyric acid can be detected, which appears early in the course of diabetic ketoacidosis.[6] The lower urinary excretion of ketones with SGLT-2 inhibitors may limit the use of urine ketones, because only acetoacetic acid can be detected.[6]

If ketones are present, SGLT-2 inhibitors should be withheld, and patients should maintain hydration and carbohydrate consumption to allow full-dose insulin therapy until ketosis is resolved. Insulin may be required for patients with type 2 diabetes who are not already taking insulin. Patients whose condition deteriorates or who are unable to tolerate oral intake of fluids or medications should present to the emergency department.[3]

When the precipitant of an atypical presentation of diabetic ketoacidosis has resolved or been rescinded, the SGLT-2 inhibitor can be restarted once the patient's condition is stable.[6] If no other cause for ketoacidosis was identified, patients should not continue taking SGLT-2 inhibitors to avoid the recurrence of ketosis. However, the decision to restart any SGLT-2 inhibitor after an episode of diabetic ketoacidosis remains controversial. These recommendations have been conveniently summarized with the acronym "NO FIGS" (Box 1).[3] Patients may also refer to a sick-day protocol available from the Canadian Diabetes Association.[3] In addition, SGLT-2 inhibitors should be stopped three days before elective surgery. For emergency surgeries, the patient should receive insulin and dextrose intravenously to prevent ketone formation.

Box 1: Canadian Diabetes Association "NO FIGS" sick day protocol[3]

Prevention of diabetic ketoacidosis among patients with type 2 diabetes mellitus who are taking a sodium–glucose cotransporter-2 (SGLT-2) inhibitor

- **N**o symptoms, do not check for ketones
- **O**nly when symptomatic*, check for ketones†, even if blood glucose is relatively low (i.e., < 14 mmol/L)
- **F**luid maintenance (mineral drinks to replace ongoing electrolyte losses in the urine)
- **I**nsulin supplementation (may need regular insulin with a sliding scale coverage, or basal intermediate or long-acting insulin)
- **G**lucose and carbohydrate intake to allow for adequate insulin dosing
- **S**GLT-2 inhibitor therapy placed on hold until ketoacidosis has resolved and the precipitant has been removed; at which time the SGLT-2 inhibitor may be restarted; if no precipitant is identified, do not restart SGLT-2 inhibitor

*Nausea, vomiting, abdominal pain, tiredness, hyperventilation or Kussmaul breathing, somnolence and confusion.

†Serum ketone detection may be preferred over urine ketone detection.

Case revisited

Despite the intense stress of cardiovascular surgery and the lingering effect of the SGLT-2 inhibitor, our patient did not have diabetic ketoacidosis while in hospital, likely because adequate hydration, glucose and insulin therapy offset a profound ketogenic burden. However, as an outpatient, the patient's mild pneumonia

precipitated ketoacidosis by creating a relative insulin-deficient state in the context of his SGLT-2 inhibitor. Patient education and a timely sick day protocol may have averted this complication.

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