Euglycemic diabetic ketoacidosis in type 2 diabetes treated with a sodium-glucose cotransporter-2 inhibitor

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More than 10 million Canadians are currently living with diabetes.[1] Of those, 90% have type 2 diabetes mellitus (T2DM).[1] Recently launched oral medications known as sodium-glucose cotransporter-2 (SGLT2) inhibitors were approved by the US Food and Drug Administration (FDA) in 2013 for treating T2DM.[2] Approval by Health Canada was granted in 2014.[3] Treatment with SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) has been shown to improve weight loss and glycemic control and to provide cardiovascular protection.[4] Given the favourable clinical profile of SGLT2 inhibitors, health care providers are increasingly prescribing these antihyperglycemic agents. However, recent FDA and Health Canada warnings have cautioned about the possibility of patients developing ketoacidosis with their use.[5,6] More important, most cases of ketoacidosis occurred in settings of mildly elevated or normal blood glucose levels (ie, euglycemic diabetic ketoacidosis [DKA]).[6] We report a case of ketoacidosis in a patient with T2DM, taking canagliflozin, presenting with a serum glucose level of 11.9 mmol/L.

Case

A 51-year-old man with a known history of T2DM and hypertension presented to the emergency department with a 1-week history of malaise, cough, and intermittent shortness of breath. Over the preceding 2 days, he admitted to a history of decreased oral intake and fever, and he had abstained from taking his antihyperglycemic medications (canagliflozin and linagliptin-metformin). He reported 3 episodes of clear emesis the day of his presentation in the emergency department. He denied any other symptoms, sick contacts, or travel history. He reported no substance use, alcohol consumption, or other ingestions. He was not vaccinated against the flu. He was not taking insulin.

Vital signs at triage were within normal limits except for a heart rate of 122 beats/min. The patient looked well and was in no acute distress. The only relevant physical examination findings were mild inspiratory crackles at the left lower lobe on auscultation of the lungs.

A 12-lead electrocardiogram showed sinus tachycardia at 101 beats/min. Initial bloodwork revealed a hemoglobin level of 159 g/L (normal range 130 to 170 g/L); a white blood cell count of 12.1×10^9/L (normal range 4.8×10^9/L to 10.8×10^9/L); a neutrophil count of 11.0×10^9/L (normal range 2.0×10^9/L to 7.0×10^9/L); a platelet count of 405×10^9/L (normal range 130×10^9/L to 400×10^9/L); a random blood glucose level of 11.9 mmol/L (normal range 3.9 to 11.2 mmol/L); a sodium concentration of 139 mmol/L (normal range 136 to 144 mmol/L); a potassium level of 5.0 mmol/L (normal range 3.5 to 5.5 mmol/L); a chloride level of 93 mmol/L (normal range 98 to 109 mmol/L); a total CO_2 level of 8 mmol/L (normal range 22 to 29 mmol/L); an anion gap of 38 mmol/L (normal range 4 to 12 mmol/L); a urea level of 9.3 mmol/L (normal range 1.7 to 8.3 mmol/L); a creatinine level of 111 µmol/L (normal range 62 to 106 µmol/L); and an estimated glomerular filtration rate of 61 mL/min. Given the abnormal anion gap and total CO_2 level, venous blood gas analysis, urinalysis, and repeated measurement of electrolytes were ordered. Venous blood gas analysis showed a pH of 7.15 (normal range 7.32 to 7.42), PCO_2 of 3.9 kPa (normal range 5.5 to 6.8 kPa), and a plasma

EDITOR'S KEY POINTS

- Ketoacidosis in the setting of sodium-glucose cotransporter-2 inhibitor use has an unclear pathophysiology and can be difficult to diagnose.
- Do not be reassured by stable vital signs, nonspecific symptoms, and a relatively normal blood glucose level. Obtain ketone levels in all suspected cases of diabetic ketoacidosis.
- Patients taking sodium-glucose cotransporter-2 inhibitors should be monitored closely and counseled regarding the symptoms (nausea, vomiting, abdominal pain, tachypnea, lethargy) and triggers (alcohol use, infection, reduced oral intake) of diabetic ketoacidosis.

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bicarbonate level of 10 mmol/L (normal range 22 to 30 mmol/L). Results of urinalysis showed large elevations in ketone and glucose levels and a small elevation in protein levels, and there were negative findings for nitrites and leukocytes. There was a large elevation in plasma ketone level. Lactic acid, liver enzyme, creatine kinase, and troponin T levels were all normal. Findings from chest x-ray scans were later reported as "Early left lower lobe infiltrate cannot be excluded."

The patient was promptly started on intravenous fluids and an insulin drip, pending his transfer to the intensive care unit for management of ketoacidosis.

Retrospective chart review revealed that the patient had been diagnosed with T2DM 8 years ago. He was taking 300 mg of canagliflozin daily, which was increased from 100 mg daily 8 months ago. No DKA or other complications had been documented since initiation of therapy. His other medications were oral combination linagliptin (2.5 mg) and metformin (1000 mg), 1 pill twice daily; 8 mg of oral perindopril daily; 20 mg of oral atorvastatin daily; and 81 mg of oral acetylsalicylic acid daily.

Discussion

Diabetic ketoacidosis is a serious diabetic emergency. Mainly occurring in patients with type 1 diabetes, it is characterized by a triad of hyperglycemia (>13.9 mmol/L), elevated urine and serum ketone levels, and anion gap acidosis (arterial blood pH <7.3).[7] Serum bicarbonate levels are typically less than 15 mmol/L.[7] *Euglycemic DKA,* defined as DKA without marked hyperglycemia, is considered to be rare, although this might be owing to underrecognition and under-reporting.[2,6,8] Left untreated, DKA can lead to serious complications including hypokalemia, acute kidney injury, cerebral edema, acute respiratory distress syndrome, shock, and even death.[9] For this reason, timely treatment is crucial and entails prompt initiation of intravenous fluids, regular insulin infusion, and monitoring of electrolyte abnormalities. Blouin provided further details on management of diabetic ketoacidosis in adults in a previous issue of *Canadian Family Physician*.[7]

The SGLT2 inhibitors have been available on the North American market since 2013.[2] Canagliflozin was the first to be approved in Canada in 2014, followed by dapagliflozin and empagliflozin, which were introduced in 2015.[3] Acting on the proximal renal tubules, these drugs prevent reabsorption of glucose from primary urine.[2] A recent randomized controlled trial of SGLT2 inhibitors showed similar or even better efficacy in reducing fasting blood glucose, body weight, hemoglobin A_{1c} levels, and blood pressure compared with mainstay agents (metformin, sulfonylureas, and sitagliptin).[3] Moreover, the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) reported remarkable reduction in cardiovascular and all-cause mortality with empagliflozin.[3] Common adverse events are genitourinary infections and orthostatic hypotension. Because the mechanism of action is not insulin dependent and because the risk of hypoglycemia is low, SGLT2 inhibitors are seen as valuable adjunctive agents to T2DM management.[8] However, according to the FDA, between March 2013 and June 2015, 73 cases of ketoacidosis requiring hospitalization were reported in patients taking SGLT2 inhibitors.[6] The median time to onset of symptoms was 43 days (range of 1 to 365 days).[6] Since then, more reports have been released documenting this phenomenon, with most cases presenting with a blood glucose level of less than 13.9 mmol/L (median of 11.7 mmol/L).[6,8] Potential ketoacidosis-triggering factors were identified in only half of cases.[4,6] These included acute illness, urosepsis, trauma, reduced oral intake, hypovolemia, acute renal impairment, and alcohol use.[6,8,10] Similarly, a search of the Canada Vigilance Adverse Reaction Online Database identified a total of 106 cases of ketoacidosis (88 for canagliflozin and 18 for dapagliflozin) occurring between December 2014 and December 2015.[11] This prompted a public health advisory and a query by Health Canada launched in June 2015 to determine whether changes were needed in prescribing this class of medications.[5] In May 2016 Health Canada issued an alert highlighting the link between SGLT2 inhibitors and DKA and is working with the manufacturers to update the product monographs.[12]

There are multiple proposed theories exploring the link between SGLT2 inhibitors and ketoacidosis. One possible mechanism describes a decreased secretion of insulin from pancreatic cells in a response to the lowering of blood glucose via urinary excretion.[2] This results in a decrease of circulating insulin and its antilipolytic activity, leading to increased free fatty acid production.[2] Other evidence suggests that SGLT2 inhibitors stimulate the secretion of the counterregulatory hormone glucagon, which in turn contributes to the overproduction of ketone bodies.[13,14] Another animal study suggests that SGLT2 inhibitors might decrease the renal clearance of ketone bodies.[2] The net result is a stimulation of the ketogenesis pathway and an increase in serum ketones, which predispose the body to ketoacidosis. This effect is compounded in the event of physiologic stressors including, for example, starvation or dehydration.[6,8,10] Although research on the pathophysiology is currently ongoing and no definitive causation has been established, the association between SGLT2 inhibitors and DKA cannot be ignored.

Going back to our case, it must be emphasized that ketoacidosis in the context of SGLT2 inhibitor therapy can be challenging to diagnose. Our patient presented

with signs, symptoms, and initial bloodwork findings suggestive of an upper respiratory tract infection. His vital signs were stable with a mildly elevated random blood glucose level (11.9 mmol/L). As this was a patient with T2DM strictly taking oral medications, the clinical suspicion for DKA was quite low. Had the serum glucose level been considered on its own without repeating his biochemical profiles and obtaining ketone levels, a provisional diagnosis of pneumonia would have been given, and the patient would have been discharged home with oral antibiotics. Consequently, the diagnosis of ketoacidosis would have been missed, potentially leading to the detrimental outcomes mentioned above. Fortunately for the patient, he presented to the emergency department, where access to further investigations was readily available. Following confirmation of ketoacidosis, the patient was admitted to the intensive care unit and managed appropriately. His acidosis and anion gap corrected over the following 2 days. He was discharged taking subcutaneous insulin, and his oral antihyperglycemics were discontinued until further assessment by his endocrinologist. The case was reported to Health Canada.

Conclusion

Ketoacidosis is a rare but serious side effect of SGLT2 inhibitors. Although occurring in less than 1% of cases,[15-17] it is increasingly being reported as these drugs become more common in medical practice. Its atypical presentation and occurrence in a relatively euglycemic state might mislead physicians. Until further research clarifies this issue, clinicians must maintain a high index of suspicion and a low threshold for obtaining ketone levels in patients taking SGLT2 inhibitors. This is especially true in the setting of recent therapy initiation, acute illness, or signs and symptoms suggestive of DKA. Doing so will ensure prompt diagnosis and treatment of this life-threatening entity, which might be otherwise missed by relying solely on blood glucose levels.

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Competing interests
None declared

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