SGLT2 Inhibitor–Induced Ketoacidosis in a Patient Without Diabetes

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are now an established treatment for heart failure, irrespective of diabetes status (1,2). The practice-changing development has led to widespread uptake of the agents by a range of specialists and primary care physicians. The risk of diabetic ketoacidosis with their use for type 2 diabetes is established, with methods in place for management (3). In contrast, the development of ketoacidosis in patients without diabetes was not reported in clinical trials for heart failure, and mechanistically it is thought to be unlikely (4). We report a case of ketoacidosis in a patient without diabetes after recent commencement of an SGLT2 inhibitor for cardiac failure.

A 78-year-old woman was admitted to hospital with a 12-h history of confusion and vomiting. No clear trigger for the event was apparent, and she was well until the day of presentation. Laboratory results revealed metabolic ketoacidosis with a pH of 7.19, bicarbonate of 10 mmol/L, and β-hydroxybutyrate of 4.0 mmol/L (Table 1). Interestingly, her venous blood glucose level at the time of admission was 2.3 mmol/L. Her medical history included cardiac failure with a left ventricular ejection fraction of 20–30%, treated with bisoprolol and sacubitril/valsartan. She had commenced empagliflozin 10 mg daily 3 weeks prior. There was no known history of diabetes. HbA_{1c} was normal at 4.5% (26 mmol/mol). She was managed in intensive care with an intravenous insulin infusion totaling 20 units in the first 24 h, supported by concurrent 10% dextrose at 20–80 mL/h. Ketosis and acidosis resolved within 12 and 21 h, respectively, and delirium significantly improved. She was treated empirically for infection with ceftriaxone, given her mildly elevated inflammatory markers, although a source of infection was not identified. Two days after admission, her predinner and fasting capillary glucose levels were 7.9 and 7.2 mmol/L, respectively.

We report one of the first cases of SGLT2 inhibitor-induced ketoacidosis in a patient without diabetes, likely due to the combination of reduced glucose availability (dietary and from glycogen stores) and resultant inadequate insulin secretion in the setting of critical illness. The high C-peptide–to–insulin ratio is suggestive of enhanced empagliflozin-induced insulin clearance, which itself may have contributed to relative lower circulating insulin

Table 1—Laboratory data on presentation

	Value	Reference range
HbA_{1c} (%)	4.5	<5.9
HbA_{1c} (mmol/mol)	26	<41
Venous blood glucose (mmol/L)	2.3	3.0–7.8
Plasma insulin (mU/L)	2.9	2.0–15.0
C-peptide (pmol/L)	2,287	200–1,200
β-Hydroxybutyrate (mmol/L)	4.0	<0.6
pH	7.19	7.32–7.42
CO_2 (mmHg)	30	38–52
Potassium (mmol/L)	3.7	3.5–5.0
HCO_3 (mmol/L)	10	24–31
Lactate (mmol/L)	0.9	0.0–2.2
C-reactive protein (mg/L)	17.8	<5.0
White blood cells ($\times 10^9$/L)	17.6	4.0–11.0
Urinary glucose	Not detected	
Urinary ketones	Not detected	
Urine culture	No growth	
Blood culture (two samples)	No growth	

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and ketoacidosis. The development of mild hyperglycemia once the SGLT2 inhibitor was eliminated is suggestive of inadequate β-cell function to prevent ketosis. Given the increasing use of this class of medications in patients without diabetes, all clinicians should be able to recognize ketoacidosis and to counsel patients to mitigate the risk.

Known precipitants for ketoacidosis with SGLT2 inhibitor use include infection or fasting for procedures (5). However, the sudden onset of severe illness and lack of clear precipitant in this case highlights that risk factors for ketoacidosis are not always evident. Hence, broad patient and physician education and awareness of this potential adverse event are important. The temporal relationship between commencement of the agent and this illness may indicate a predisposition of some patients, and further pharmacovigilance is required to help in identifying those at risk.

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