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Severe ketoacidosis in a patient taking an SGLT2 inhibitor for diabetes

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Diabetic ketoacidosis is rarely seen in patients with type 2 diabetes. Doctors and patients need to be aware that sodium-glucose cotransporter 2 (SGLT2) inhibitors increase the risk of diabetic ketoacidosis, also in patients with type 2 diabetes. Here we present the case of a woman in her forties hospitalised with severe diabetic ketoacidosis while undergoing treatment for a presumed type 2 diabetes.

A woman in her forties awoke with a worsening of dyspnoea that started the previous evening. An ambulance was called, and on arrival the patient was awake, alert and oriented. Her respiratory rate was >20 per minute, heart rate 115 beats/min, blood pressure 135/80 mm Hg and glucose level 13.6 mmol/l. The hospital doctor consulted, advised the patient to contact her general practitioner. She was given an emergency appointment at the daytime emergency service. The examination revealed a heart rate of 100 beats/min, but otherwise normal status. Glucose readings were not performed and the patient was sent home. Six

hours later, she was found comatose by her partner, and was admitted to hospital, following a 999 call.

The patient was examined by a medical team in the emergency department. She was unconscious, with a Glasgow Coma Scale (GCS) score of 4, temperature 35.3 °C (tympanic), blood pressure 90/54 mm Hg, heart rate 127 beats/min, respiratory rate 24 per minute and glucose level 25.3 mmol/l. Her pupils were dilated and unresponsive to light. Cardiac and pulmonary status were normal.

The patient had been diagnosed with a presumed type 2 diabetes eight years earlier treated with vildagliptin 50 mg × 2, metformin 1 000 mg × 2, glimepiride 2 mg × 1 and dapagliflozin 10 mg × 1 (for the last three years). She was otherwise healthy and in full-time employment, but had felt generally below par in the weeks prior to the admission.

Arterial blood gas showed severe metabolic acidosis with pH 6.69 (7.35–7.45), HCO_3^- 1.1 mmol/l (22.0–26.0), base excess (BE) −31 mmol/l (−3–+3), anion gap 18.0 mmol/l (3–11), chloride 116 mmol/l (98–108), lactate 1.2 mmol/l (0.0–2.4). Urine dipsticks showed ketones 3+ and glucose 4+. Laboratory tests revealed leukocytes $20.1 \cdot 10^9$/l (3.5–8.8), CRP 1 mg/l (<5), and normal liver and kidney function, while chest X-ray and head CT were also normal.

The patient was treated in the medical observation and assessment unit. Over the first 24 hours, she received intravenous therapy with a total of 4 500 ml sodium chloride 9 mg/ml, 375 mmol bicarbonate, 83 IU insulin and 230 mmol potassium chloride. She did not require respiratory or vasopressor support. She gradually regained consciousness over the course of the first few hours and was transferred to a general ward the day after her admission. After 48 hours, pH was 7.37 (7.35–7.45) and HCO_3^- was 16.3 mmol/l (22.0–26.0). HbA1c was 112 mmol/mol (20–42) (12.4 %).

Subcutaneous insulin injection was started, and the patient was discharged in good general condition after four days, with intermediate-acting insulin 16 IU in the morning and 8 IU in the evening with dose escalation. Vildagliptin and metformin were continued, while dapagliflozin and glimepiride were discontinued.

Test results received afterwards showed positive anti-GAD and low C-peptide levels. These findings are consistent with undiagnosed latent autoimmune diabetes in adults (LADA) and not type 2 diabetes as had been presumed.

Discussion

Diabetic ketoacidosis is a serious condition that can be life-threatening if left untreated. In the setting of SGLT2 inhibitor use, diabetic ketoacidosis is associated with mild hyperglycaemia, and the patient may develop euglycaemic ketoacidosis with blood glucose <11.1 mmol/l (1). The incidence of diabetic ketoacidosis in the setting of SGLT2 inhibitor use is 9.4 % in type 1 diabetes and <0.2 % in type 2 diabetes (2). These data are from studies in which the patients are closely monitored.

Dapagliflozin, which our patient was taking, is an SGLT2 inhibitor that was introduced in Norway in 2012. Other SGLT2 inhibitors in use in Norway are empagliflozin, canagliflozin and ertugliflozin. SGLT2 inhibitors are increasingly prescribed because of their ability to lower blood glucose, blood pressure and weight, and because of their favourable cardiorenal profile. Several studies have shown this class of drugs to reduce the incidence of cardiovascular events and death, as well as hospitalisations owing to heart failure (2).

The Norwegian national guidelines for diabetes recommend that for patients with type 2 diabetes and known cardiovascular disease, SGLT2 inhibitors should be used as a second-line treatment (like GLP-1 analogues) in combination with metformin (3).

Our patient had very poorly controlled diabetes and thus a clear indication for insulin therapy. It later transpired that the patient had LADA, which is often misdiagnosed as type 2 diabetes. The cause of the severe ketoacidosis was assumed to be failure of insulin

production in the setting of SGLT2 inhibitor use (Box 1).

Box 1 Key facts about SGLT2 inhibitors and ketoacidosis. Based on Karslioglu (1) and Diaz-Ramos (2) as well as the authors' own experience.

- Symptoms of diabetic ketoacidosis include reduced general condition, nausea, abdominal pain, thirst, polyuria, confusion and hyperventilation
- Anti-GAD and C-peptide should be measured in cases of newly discovered type 2 diabetes to assess the risk of LADA
- An SGLT2 inhibitor should be paused immediately if there is a risk of diabetic ketoacidosis (dehydration, infection, surgery)
- Exercise caution with the use of SGLT2 inhibitors in patients with limited insulin production (type 1 diabetes/LADA/long-duration type 2 diabetes/pancreatitis). Consider measuring C-peptide.
- Other risk factors for SGLT2-associated ketoacidosis are reduced insulin dose, alcohol abuse, a low carbohydrate diet and certain medications.
- If acute symptoms arise upon use of an SGLT2 inhibitor, it is essential to rule out (euglycaemic) ketoacidosis

SGLT2 inhibitors reduce blood glucose levels by excreting glucose via the kidneys. This is achieved by means of the drug binding to sodium-glucose cotransporter-2 (SGLT2) in the proximal tubules, leading to increased renal glucose excretion and thus lower glucose levels. This in turn results in lower insulin levels, with increased lipolysis and increased levels of ketone bodies. The renal reabsorption of ketone bodies is also upregulated. In addition, SGLT2 inhibitors stimulate glucagon production, which increases ketone body levels and hepatic glucose production. In SGLT2 inhibitor-induced diabetic ketoacidosis, very low bicarbonate levels may therefore be seen (Table 1) in addition to both euglycaemic and hyperglycaemic ketoacidosis (Figure 1) (2).

Table 1

Comparison of findings in SGLT2 inhibitor-induced and classic diabetic ketoacidosis, based on Dizon (5).

Biochemistry	SGLT2-induced diabetic ketoacidosis	Classic diabetic ketoacidosis
S-glucose	Normal/↑	↑↑
pH	↓↓	↓
Bicarbonate	↓↓	↓

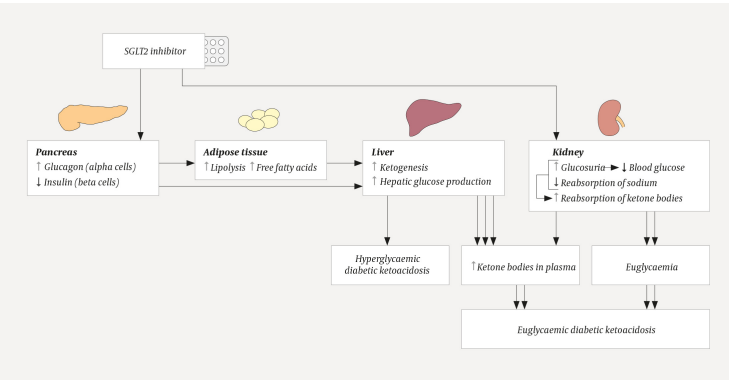

Figure 1 *Possible mechanisms underlying SGLT2 inhibitor-induced euglycaemic/hyperglycaemic ketoacidosis, based on Singh (4).*

This case report illustrates the importance of clinicians and patients being aware of the increased risk of diabetic ketoacidosis upon use of SGLT2 inhibitors in both type 1 and type 2 diabetes, as well as the fact that minimal hyperglycaemia can often result in a delayed diagnosis. At Akershus University Hospital, we have seen an increasing incidence of severe diabetic ketoacidosis in patients with type 2 diabetes over the past couple of years, and assume that SGLT2 inhibitors have been a contributing factor.

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