



SGLT2 Inhibition May Precipitate Euglycemic DKA after Bariatric Surgery

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Abstract

SGLT2 inhibitors (SGLT2Is) lower blood glucose through inhibition of glucose reabsorption in the proximal renal tubules via an insulin independent mechanism. They have a low risk of hypoglycaemia with additional benefits including weight loss, blood pressure reduction and cardiovascular protection [1]. Euglycaemic diabetic ketoacidosis (euDKA) is a rare complication of SGLT2Is observed in patients with both type 1 and type 2 diabetes and can be easily overlooked by medical care providers because of the absence of marked hyperglycaemia. In type 2 diabetes, this complication was reported in the post-operative setting, mostly occurring within two weeks after surgery. We report a case of euDKA precipitated by using SGLT2Is in a patient with type 2 diabetes occurring six weeks after bariatric surgery. This case highlights the importance of stopping these agents beyond the immediate post-operative period following bariatric surgery as weight loss is itself a stimulus for ketone production.

Case Report

A 45-year-old woman with a five year history type 2 diabetes presented with a two day history of abdominal pain associated with, nausea, decreased appetite, malaise and shortness of breath without constitutional symptoms. Her past medical history included hypertension, hyperlipidaemia and reflux oesophagitis. She never had DKA, never consumed alcohol and she did not take large amount of soft drinks prior to presentation. She had no history of recent illness except for low back pain which was treated with a local steroid injection and non-steroidal anti-inflammatory drugs (NSAIDs) a few days previously. She underwent sleeve gastrectomy 6 weeks prior to presentation and lost 18 kilograms in weight since surgery with a current body mass index of 38.58 Kg/m². She was taking Amlodipine 5 mg daily, Dapagliflozin 10 mg daily and Esomeprazole 20 mg daily.

On clinical examination she looked unwell with a normal temperature of 37.0 °C, pulse rate 95/minute regular, blood pressure 112/63, oxygen saturation (SPO₂) 100% on air. Systemic examination was unremarkable apart from mild epigastric tenderness. Investigations revealed a leucocytosis (white blood cell count 14.53 × 10⁹/L, neutrophil 78.3%) with a normal C-reactive protein (CRP) of

4.25 mg/L (0-4.9). She had a high anion gap metabolic acidosis with a low serum bicarbonate of 8.53 mmol/L, an anion gap of 22.4, arterial pH 7.12, blood glucose 10.19 mmol/L, HbA1c 7.5%, sodium 135.9 mmol/L, potassium 3.31 mmol/L, chloride 105 mmol/L, urea 3.1 mmol/L, creatinine 56.2 µmol/L (50-88). Urinalysis showed increased glucose, increased ketones of 15 mmol/L (0-0.49) and no evidence of infection or casts. Liver function test, serum lactate and amylase were normal. C-peptide was detectable at 0.388 nmol/L (0.37-1.47). GAD and IA2 antibodies were negative. Chest X-ray, electrocardiogram, computed tomography (CT) of chest and abdomen were normal. Gastroscopy revealed oesophagitis. She was treated with intravenous fluids and insulin in the intensive care unit and made a full recovery within 72 hours of admission. She was discharged home on a basal bolus insulin regime which was gradually phased out to a once daily basal insulin regime over a few weeks period.

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Discussion

Diabetic ketoacidosis is a potentially fatal complication of diabetes and is classically defined as a triad of hyperglycaemia with a blood glucose level of > 250 mg/dL (13.9 mM), metabolic acidosis (arterial pH < 7.30 and serum bicarbonate < 15 mEq/L) and ketosis [2]. Euglycaemic diabetic ketoacidosis (euDKA) is a relatively uncommon subset of ketoacidosis with less marked hyperglycaemia and could be easily missed because the relatively normal glucose level and lack of significant clinical symptoms may mask its recognition by both patients and physicians.

There is increasing evidence suggesting the link between euDKA and the use SGLT2Is. In the first published case series, 13 cases of euDKA were described among patients with type 1 and type 2 diabetes. Only two of these patients had type 2 diabetes and in both euDKA occurred postoperatively [3]. Subsequent case reports were largely among patients with type 2 diabetes [4,5].

The exact mechanism by which SGLT2Is cause euDKA remains unclear and is likely to be multifactorial. First, decreased insulin secretion due to lowering of blood glucose is thought to contribute to lipolysis and increased fatty acid secretion and subsequent ketone production [6]. Secondly, increased glucagon secretion either secondary to decreased insulin level or through a direct effect of SGLT2Is on pancreatic α -cells contributes to production of ketone bodies [7]. Furthermore, SGLT2Is may reduce the renal threshold for ketone body excretion [8].

Precipitants of euDKA include surgery, severe infections, extensive exercise, myocardial infarction, stroke, prolonged fasting, alcohol consumption, and other stressful physical and medical conditions. It is more common in insulin deficient individuals, such as patients with type 1 diabetes, long standing type 2 diabetes or latent autoimmune diabetes (LADA) [4].

Most cases of diabetic ketoacidosis after bariatric surgery presented within the first month after surgery, and the most common symptoms were nausea, vomiting and abdominal pain which are common soon after bariatric surgery and may lead to overlooking the diagnosis of DKA and ordering unnecessary imaging studies to rule out surgical complications [9]. A few cases of post-operative euDKA due to SGLT2Is were reported, mostly occurring within 2 weeks after surgery [3]. Only one case was reported following bariatric surgery and was linked to the use of Canagliflozin [10].

Our patient who was taking Dapagliflozin, presented with euDKA six weeks following bariatric surgery while previous cases were reported much earlier. The late presentation in our patient could be explained by the pro-

longed calorie restriction and poor fluid intake following bariatric surgery. In addition, rapid weight loss and the catabolic state after metabolic surgery could have a contributory role. She was also taking amlodipine and esomeprazole which were reported to be associated with ketoacidosis and acute kidney failure respectively [11, 12]. However, amlodipine causes acidosis only when taken in an overdose, and in this patient esomeprazole is unlikely to be contributing to the acidosis in the presence of normal renal function.

This case highlights the importance of stopping SGLT2Is beyond the immediate post-operative period in patients undergoing bariatric surgery. In this group of patients, resumption of treatment with SGLT2Is should be delayed until patients are able to maintain a balanced diet with sufficient carbohydrate content and adequate fluid intake and are no longer catabolic. All patients taking SGLT2Is should be counselled about the risk of ketoacidosis during acute illness and other stressful situations such as surgery.

A high index on suspicion is needed to ensure early detection, prompt diagnosis and timely management of this potentially fatal medical emergency.

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