

Three cases of euglycaemic diabetic ketoacidosis related to the use of sodium-glucose co-transporter-2 inhibitors and calorie restriction

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Dear Sir,

Between December 2018 and February 2020, three cases of euglycaemic diabetic ketoacidosis (EuDKA) were seen in my practice (Table I). All three had Type 2 diabetes mellitus (DM). All cases involved the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors and a short period of calorie restriction a few days prior to admission to hospital. The three patients varied in age (21–60 years), duration of DM (5 days–10 years) and duration of use of SGLT2 inhibitors (5 days–3 years). None were on insulin. The calorie restriction was deliberate in two patients, who were attempting to quickly control their DM, and partially involuntary in the third, who had gastroenteritis. All developed ketoacidosis within five days of their change in diet.

The entity of EuDKA was first reported in 1973.⁽¹⁾ Reports of ketoacidosis in relation to the use of SGLT2 inhibitors began to appear in 2015.⁽²⁾ Significantly, some occurred in patients with Type 2 DM. Ketoacidosis has been reported in patients without DM and those who were not using SGLT2 inhibitors. For instance, Shah and Isley reported that a 51-year-old woman without DM developed four episodes of ketoacidosis while on a 'no carbohydrate' diet (over a period of four years) with a carbohydrate intake that was estimated to be as low as 20 g per day.⁽³⁾

Our patients were estimated to have taken about 60–90 g of carbohydrate each day and had a calorie intake of only 1,000–1,200 calories per day. They developed ketoacidosis after 3–5 days of dieting. It is likely that the suddenness of the diet as well as the insufficient calorie and carbohydrate intake contributed to the development of EuDKA in these three patients. Patients 1 and 3 had normal C-peptide and insulin levels during admission. However, very low carbohydrate intake can lead to reduction in insulin release and the relative insulinopenia could contribute to EuDKA. In Patient 2, gastroenteritis causing dehydration could be a contributing factor.

Hamblin et al reported that SGLT2 inhibitor usage increases the risk of EuDKA developing during hospital admissions.⁽⁴⁾ More users (with Type 2 DM) developed EuDKA, as an inpatient, as compared to non-users of SGLT2 inhibitors (14 cases vs. two cases). In the United Kingdom, it is advised that patients pause the use of SGLT2 inhibitors when they are hospitalised for surgery or acute illnesses; treatment with SGLT2 inhibitors may be restarted once their condition has stabilised.⁽⁵⁾ The Australian and New Zealand

Table I. Patient characteristics and clinical presentation.

Characteristic	Patient 1	Patient 2	Patient 3
Age	21 years	60 years	39 years
Duration of DM	2 years	10 years	5 days
SGLT2 inhibitor used	Empagliflozin	Dapagliflozin	Dapagliflozin
SGLT2 inhibitor duration	10 months	3 years	5 days
Duration of caloric restriction	3 days	3 days	5 days
Reason for dieting	Control of DM	Loss of appetite	Control of DM
Carbohydrate intake per day (estimated)	60 g	60 g	90 g
Calorie intake per day (estimated)	1,000 calories	1,000 calories	1,200 calories
Symptoms on admission/presentation	Vomiting, epigastric pain, shortness of breath	Vomiting, diarrhoea	Vomiting, abdominal pain
Other illness/infection	None	Gastroenteritis	None
Other DM medications	Metformin, linagliptin	Metformin, glipizide	Metformin
Blood glucose on admission	6.1 mmol/L	8.1 mmol/L	6.1 mmol/L
HbA1c	9.3%	7.5%	12.5%
Weight	78.8 kg	104.0 kg	83.5 kg
Height	1.74 m	1.64 m	1.73 m
Body mass index	26.0 kg/m ²	38.7 kg/m ²	27.9 kg/m ²
Urine ketones	3+	3+	3+
Bicarbonate (normal 21–32 mmol/L)	< 10 mmol/L	16 mmol/L	< 10 mmol/L
Blood ketones (normal 0–0.6 mmol/L)	5.6 mmol/L	Not tested	6.0 mmol/L
C-peptide (normal 0.78–5.19 ng/mL)	1.68 ng/mL	Not tested	2.26 ng/mL
Insulin (normal 1.8–13.8 mIU/L)	8.3 mIU/L	Not tested	6.7 mIU/L
GAD antibody	Negative	Not tested	Negative

DM: diabetes mellitus; GAD: glutamic acid decarboxylase; HbA1c: glycated haemoglobin; SGLT2: sodium-glucose co-transporter-2

College of Anaesthetists recommends that SGLT2 inhibitors be stopped up to three days preoperatively (two days prior to and on the day of surgery) or in other physically stressful situations.⁽⁶⁾

We should be mindful that patients on SGLT2 inhibitors may develop EuDKA in situations where calorie intake is temporarily curtailed. With low carbohydrate diets, ketogenic diets, intermittent fasting and other forms of calorie restriction becoming more popular, we may begin to see the entity of EuDKA more often.

Yours sincerely,

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