Title: Letter to the editor; **A case series of DKA occurring in patients receiving treatment with SGLT-2 inhibitors**

List of authors for the letter to editor

Name	**Affiliations**
Dr Jawad Bashir	Speciality Registrar diabetes and endocrinology, University Hospital of Wales, Cardiff, CF14 4XW
Dr Preethi Nalla	Speciality Registrar diabetes and endocrinology, University Hospital of Wales, Cardiff, CF14 4XW
Dr Rajesh Peter	Consultant diabetes and endocrine, Singleton Hospital, Swansea SA2 8QA
Professor Stephen C Bain	Diabetes Research Group, School of Medicine, Swansea University SA2 8PP
Dr Richard Chudleigh	Consultant diabetes and endocrine, Singleton Hospital, Swansea SA2 8QA

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To the editor

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are increasingly used in the management of type 2 diabetes (T2DM) due to their effective glucose-lowering and secondary benefits of weight loss, blood pressure reduction and low risk of hypoglycaemia.[1] In 2015, the US food and drug administration (FDA) reported 21 cases of diabetic ketoacidosis (DKA) associated with SGLT-2i use via the FDA Adverse Event Reporting System (FAERS). 102 events were subsequently identified by the European Medicines Agency (EMA) from EudraVigilance.[2, 3] Since then several case reports have been published [4-15] and DKA is now a recognised rare side-effect of SGLT-2i (1 in 1000). [16]

Here we report eight cases of DKA in association with SGLT-2i use; 5 with dapagliflozin, 2 with canagliflozin and 1 with empagliflozin (see table-1 in addendum). These occurred in a catchment population of about 500,000 in the United Kingdom over a period of one year with a background prevalence of 7% for type 2 diabetes in adults and 8.4% patients being treated with SGLT-2i.[17] All cases had previously been labelled as having T2DM, with a mean duration of diabetes of 16.75 (range 9-30) years. They were commenced on SGLT-2i for poorly controlled glycaemia (mean HbA1c = 99 ± 28 mmol/mol [11.2 ± 4.7 %]) on a background of obesity (mean BMI = 34.31 kg/m^2).

All cases had been on SGLT-2i for approximately 3 months before presenting with DKA, with the exception of # 1 who developed DKA after 13 days treatment with dapagliflozin; in this case the patient had erroneously stopped all her insulin (100 units daily dose) when dapagliflozin was initiated. Seven patients were over the age of 50 years, the exception being #5, a 37 year old woman with previous gestational diabetes which had progressed to T2DM (BMI 35.1 kg/m^2; HbA1c 133 mmol/mol [14.3%]). She developed severe DKA associated with dental sepsis after being switched to dapagliflozin monotherapy from the triple combination of metformin, exenatide and insulin (96 units daily dose).

The only case not to be initially treated with insulin was a 70 year old woman (# 6) with T2DM for 30 years who was managed on metformin and sitagliptin. She developed DKA as an in-patient following an extended period of fasting whilst awaiting surgical drainage of bilateral axillary abscesses.

Three of the subjects subsequently tested positive for anti-GAD antibodies, suggesting a diagnosis of latent autoimmune diabetes in adults (LADA). In two of these cases (# 3 & 7) insulin had been initiated in the same year as their diabetes diagnosis and one (case # 2) had experienced previous episodes of DKA; these clinical features are consistent with LADA, for which SGLT2i are not currently licenced.

One case (#4) had previous history of idiopathic pancreatitis and gastroparesis who tolerated SGLT-2i for more than 3 years before presenting with DKA precipitated by vomiting with flare up of gastroparesis.

None of the DKA cases presented with normal or subnormal blood glucose (<11 mmol/L; 200 mg/dL) which has been reported in around 60% of case reports (so-called 'euglycaemic DKA') and six presented with a blood glucose higher than 20 mmol/L (360 mg/dL). Two cases (case # 4 & 8) were detected before developing overt DKA (pH 7.32 and 7.31) but had raised capillary ketones (7.3 and 2.2 mmol/L). In all cases DKA resolved within 24 hours with a standard protocol using intravenous insulin and fluids and intensive care was not required. A recognised precipitant of DKA was identified in all cases (see table-2 in addendum) and the SGLT-2i was with-held with no re-challenge.

The exact mechanism of DKA with SGLT-2i use is incompletely understood but mild asymptomatic ketonaemia is an effect of SGLT-2i. This may be due to increased fatty acid utilization with SGLT-2i resulting from a reduction of the insulin to glucagon ratio and also increased urinary ketone absorption.[18-20] We recommend caution when prescribing SGLT-2i for middle-aged and elderly patients on high dosages of insulin and rapid reduction of insulin should be discouraged. 'Sick day rules' should be applied with the temporary cessation of SGLT-2i therapy during any episode of vomiting and reduced oral intake. The drug regulatory bodies and expert societies suggest not to restart SGLT-2i in a patient who experiences an unprovoked episode of DKA.[16, 21, 22] The presence of conventional risk factors for DKA along with SGLT-2i usage should alert clinicians to discontinue this drug temporarily to avoid this preventable but life-threatening complication. Patient education and provision of alert cards is good clinical practice when prescribing this drug class.

Table-1-A and 1-B: Eight cases of DKA associated with SGLT-2i use presenting locally (please see addendum)

Table-2: List of recognised risk factors for diabetic ketoacidosis (please see addendum)

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Table:1-A; Eight cases of DKA associated with SGLT-2i use presenting locally (Anti-GAD antibody negative)

No (Age)	**Age at diagnosis and duration of diabetes**	**Anti-GAD Antibodies** †	**SGLT-2i (Duration of use)** ‡	**BMI (kg/m²)**	**Prior Insulin use (Type)**	**Insulin Regime (Total daily dose)** §	**Insulin dose reduced (Amount)**	**Concomitant drugs**	**Prior HbA1c mmol/mol**	**Potent precipita DKA**
Case 1 (59yr)	42 & 17yrs	Negative	DAPA (13 days)	34.2	Yes (Humalog Mix 50)	Biphasic insulin BD (100 units)	Yes (100 units)	Metformin, Liraglutide	128	Stopped i (100un
Case 4 (52yr)	37 & 15yrs	Negative	DAPA (1145 days)	28.4	Yes (Degludec & Novorapid)	Basal bolus regime (134 units)	No (0 units)	Metformin	94	Gastropa
Case 5 (37yr)	27 & 10yrs	Negative	DAPA (170 days)	35.1	Yes (Humulin M3)	Biphasic insulin BD (96 units)	Yes (96 units)	Metformin, Exenatide, Gliclazide (stopped all)	133	Dental se with-held
Case 6 (70yr)	40 & 30yrs	Negative	CANA (121 days)	39.4	No	Not applicable	Not applicable	Metformin, Sitagliptin	86	Prolonge operative
Case 8 (59yr)	50 & 9yrs	Negative	EMPA (90 days)	42.6	Yes (Novomix 30)	Biphasic insulin BD (112 units)	Yes (60 units)	Metformin, Gliclazide, Liraglutide	80	SAIO Right hemicole (post-c

Table 1-B; Eight cases of DKA associated with SGLT-2i use presenting locally (Anti-GAD antibody positive)

No (Age)	**Age at diagnosis and duration of diabetes**	**Anti-GAD Antibodies †**	**SGLT-2i (Duration of use) ‡**	**BMI (kg/m²)**	**Prior Insulin**	**Insulin Regime (Total daily dose)** §	**Insulin dose reduction**	**Concomitant drugs**	**Prior HbA1c mmol/mol**	**Poten precipita DKA**
Case 2 (59yr)	45 & 14yrs	**Positive (295U/ml)**	DAPA (80 days)	34.3	Yes (Levemir & Novorapid)	Basal bolus insulin MDI (34 units)	Uncertain	Metformin	119	Diarrh
Case 3 (51yr)	42 & 9yrs	**Strongly positive (6350U/ml)**	DAPA (87 days)	30	Yes (Humalog Mix 50)	Biphasic insulin TDS (42 units)	Yes (but dose unknown)	Metformin, Liraglutide	80	Vomi
Case 7 (64yr)	34 & 30yrs	Lightly positive (15U/ml)	CANA (90 days)	30.5	Yes (Novorapid & Lantus)	Basal bolus MDI (unknown)	Yes (stopped all)	None	72	Vomit gastroen

† Anti-GAD antibodies = Anti Glutamic acid decarboxylase antibodies

‡ DAPA = Dapagliflozin, CANA = Canagliflozin, EMPA = Empagliflozin.

§ BD = Twice daily, TDS = Thrice daily, MDI = Multiple daily injections

¶ SAIO = Subacute intestinal obstruction

Table; 2 List of recognised risk factors for diabetic ketoacidosis

- Undiagnosed T1DM/LADA (uncertain history of onset of diabetes)
- Massive reduction in insulin dosages
- Post-operative state
- Starvation/extended fasting/Low carbohydrate intake
- Gastroparesis
- Pancreatic insufficiency
- Acute stress/viral illness/severe sepsis
- Acute coronary syndrome
- Alcohol consumption
- Moderate exercise without enough carbohydrate intake
- Clinicians' misjudgement
- Elderly patients (>65 years)
- Long standing history of diabetes (>30 years)