Association of British Clinical Diabetologists (ABCD) position statement on the risk of diabetic ketoacidosis associated with the use of sodium-glucose cotransporter-2 inhibitors

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Diabetic Ketoacidosis (DKA) has been reported in patients with diabetes taking SGLT-2 inhibitor drugs both in clinical trials and in real life situations, particularly amongst patients taking insulin. The US Food and Drug Administration (FDA) has issued a safety communication following 20 cases of DKA in patients receiving these drugs.[1] This concern has also prompted an American Association of Clinical Endocrinologists and American College of Endocrinology position statement covering the use of SGLT-2 inhibitors in people with type 2 diabetes.[2] The following is the ABCD position statement on this issue.

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Risk of DKA in patients taking SGLT-2 inhibitors

The absolute risk of DKA with SGLT-2 inhibitors is unclear but the current reported incidence of SGLT-2 inhibitor associated DKA is likely to be an underestimate due to the unusual presentation of these patients and a lack of general awareness of this complication. In the cardiovascular outcome trials with this group of drugs DKA was not anticipated and hence there was no requirement to systematically look for its development which is likely to have contributed to under reporting of this complication.[3] The current clinical trial protocols in patients with type 1 diabetes require more in-depth recording of DKA.

DKA frequency in the background diabetic population has been reported to be between 0.32 and 7.1 per 1000 patient-years, of which 23-32% are thought to be in patients with type 2 diabetes.[2,4-6] Clinical trials with SGLT-2 inhibitors in type 2 diabetes reported an incidence of DKA in the range of 0.2 to 1.2 per 1000 patient-years.[2,7,8] A much higher incidence was reported in trials with type 1 diabetes.[9-15] There were 147 cases recorded in the EudraVigilance database in the post marketing phase of the SGLT-2 inhibitors.[16] A recent meta-analysis of 10 eligible RCTs involving 13,134 patients and 14 DKA events found an overall event rate of 0.1% in the SGLT-2 inhibitor group versus 0.06% in the control group (ns).[17] This data, however, is based on protocols which did not require systematic detection or reporting of DKA and hence may be an underestimate.

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High risk groups

The majority of cases of SGLT-2 inhibitor associated DKA have occurred in people with type 1 diabetes including latent autoimmune diabetes in adults (in general people with insulin deficiency). Some cases are thought to have occurred in patients with a prolonged history of type 2 diabetes and reduced beta cell reserve.[18]

In the canagliflozin clinical trials 6 of the 12 patients that developed ketoacidosis had low C-peptide levels (<0.51 ng/mL) and were positive for GAD65 autoantibodies.[2] In the American series that resulted in the FDA warning, 7 of 9 patients had type 1 diabetes.[2]

Metabolic changes

Many reported cases simply represent a shift of metabolism from a glucose-dependent one to a fat-dependent one resulting in ketonuria and ketosis and, in extreme cases, ketoacidosis. SGLT-2 inhibitors can produce this shift in people with or without diabetes leading to reduced plasma glucose and insulin levels, stimulation of endogenous glucose production and suppression of glucose disposal.[19] Full dose SGLT- 2 inhibition induces glucose excretion ranging from 50-100 g/day.[20] In a typical patient this could amount to 17-57% of carbohydrate intake.[21] In SGLT-2 inhibitor treated patients with type 2 diabetes, a lower insulin to glucagon ratio leads to nearly 40% higher lipolysis after a meal, 20% higher fat oxidation, 60% lower carbohydrate oxidation, 15% lower glycogen synthesis and two fold higher ketogenesis.[22,23] This may not necessarily be harmful and may indeed be desirable to reduce fat in the body. In fact, it has been hypothesised that preferential energy efficient utilisation of beta hydroxybutyrate as a substrate by the myocardium and kidneys may partly underlie the swift cardiovascular

and renal benefits that have been seen in the EMPA-REG trial.[24,25] Asymptomatic ketosis, which is not clinically relevant in type 2 diabetes, may become crucial in type 1 diabetes particularly if insulin dose is low and there are additional factors which promote ketogenesis.[23]

Precipitants

Usually, in the cases of DKA reported in association with SGLT-2 inhibitors, there is a precipitating factor both in patients with type 1 and type 2 diabetes. This might be surgery, exercise, myocardial infarction, stroke, severe infection, prolonged fasting, excessive alcohol consumption, serious injury, hypovolaemia, pancreatitis, marathon running or a very low calorie diet.[23] These factors may cause a stress induced shift of metabolism from carbohydrate to fat dependence.

Pathophysiology

When certain high risk patients are faced with particular metabolic stress ketone production exceeds ketone clearance from the body. There might be many pathophysiological mechanisms underlying this state including relative insulin deficiency, glucagon excess promoting a shift of metabolism towards fat, increased glycogenolysis and gluconeogenesis because of insulin lack and glucagon excess, insulin resistance increased by lipolysis, an increase in counter regulatory hormones and reduced glucose utilisation by tissues.[26]

SGLT-2 inhibition in pancreatic alpha cells may result in increased glucagon production because of reduced paracrine inhibition by insulin and SGLT mediated glucose transfer into alpha cells.[26-28]

By their effect on renal tubules SGLT-2 inhibitors may mimic starvation status and cause an increase in ketone production and renal re-absorption as has been documented with phlorizin.[26,29-33]

Lower than expected hyperglycaemia in SGLT-2 inhibition associated with DKA may be a result of a combination of factors including partial treatment of DKA, fasting or carbohydrate avoidance, dehydration, alcohol consumption and glycosuria.[34,35]

Presentation

Presentation of DKA in these patients is usually typical with classical symptoms and high glucose levels. However, some reported cases have presented with lower than expected hyperglycaemia. This type of euglycaemic, or lower than expected, hyperglycaemic ketoacidosis has previously been described.[34-36]

In the cases described to date, blood glucose levels have not been consistently reported. The lowest reported level was 5 mmol/L and 13 cases have been reported with levels below 10 mmol/L. The majority, however, had glucose levels above 13.8 mmol/L.[2] There does not appear to be a fixed level of glucose below which DKA can be excluded with certainty. Some of these patients may not be admitted directly under the care of a diabetes specialist due to the absence of hyperglycaemia.

Recommended immediate action

Diabetic ketoacidosis, which may be euglycaemic (euDKA), should be considered in all patients taking SGLT-2 inhibitors who present with typical symptoms of diabetic ketoacidosis such as abdominal pain, nausea, vomiting, fatigue, and dyspnoea and an appropriate workup should be carried out as per JBDS guidelines.[37]

Table 1 Diagnosis of DKA in patients taking SGLT-2 inhibitors[2,37]

Arterial pH	Less than 7.3
Blood ketones	Above 3 mmol/L
Anion gap	Above 10
Bicarbonate	Less than 15 mmol/L
Clinical	Deteriorating level of consciousness in severe cases

The diagnosis should not depend upon the presence of ketones in the urine (which may be false negative because of increased resorption or may be present but not associated with ketosis or ketoacidosis) or even blood ketones but should be based on low bicarbonate (<15.0 mmol/L), low pH (<7.3) and quantitative excess of blood ketones over the limit that is considered diagnostic of DKA i.e. 3.0 mmol/L. Glucose level is lowered as a result of glycosuria induced by SGLT-2 inhibitors but ketosis is exaggerated by actual or relative insulin deficiency. Glucose levels are usually higher than 11 mmol/L but can be lower and, therefore, in a person known to have diabetes the diagnosis of diabetic ketoacidosis should always be considered even if blood glucose levels are normal.[38] This is particularly relevant in patients taking SGLT-2 inhibitors (Table 1).

Further management

Once DKA is confirmed, ABCD advises to stop the SGLT-2 inhibitor immediately and treat ketoacidosis with existing Trust or JBDS protocol.[37] The focus of treatment is to correct pH, bicarbonate and the anion gap. A variable rate intravenous insulin infusion (VRIII) with dextrose and potassium rather than a fixed rate insulin infusion may be needed to avoid hypoglycaemia and hypokalaemia.

Despite stopping an SGLT-2 inhibitor the associated increase in urinary glucose loss and, therefore, fat dependent metabolism may persist for several days.

Preventing DKA in high risk patients taking SGLT-2 inhibitors

1. Avoid or stop SGLT-2 inhibitors in situations likely to shift metabolism to a catabolic state rather than anabolic state i.e. at least 24 hours prior to a major elective surgery, planned invasive procedures or an anticipated severe stressful physical or mental activity such as running a marathon. The effect on glycosuria may persist for a few days after the drug is stopped.[2]
2. The drug should also be stopped prior to emergency surgery or situations of extreme stress like major trauma.
3. Interrupt treatment with the SGLT-2 inhibitor in patients who are hospitalised for major surgery or acute serious illness. Treatment may be restarted once the patient's condition has stabilised.[39]
4. Pre-printed educational medication cards like the one in use at East and North Herts Institute of Diabetes and Endocrinology (ENHIDE) might help reduce complications of SGLT-2 inhibitors

Figure 1. An example of diabetes information card from East and North Herts Institute of diabetes and Endocrinology (ENHIDE)

Diabetes Medicine to Stop Temporarily

- Metformin
- **SGLT2 inhibitors**: names ending in '**flozin**' e.g. canagliflozin, dapagliflozin,empagliflozin
- **GLP1 analogues** (injectable): names ending in '**tide**' e.g. liraglutide , dulaglutide, lixisenatide
- **ACE inhibitors**: names ending in '**pril**' e.g. ramipril, lisinopril, perindopril
- **ARBs**: names ending in 'sartan' e.g. candesartan, losartan, irbesartan
- **NSAIDs**: anti-inflammatory pain killers e.g. ibuprofen, naproxen, diclofenac
- **Diuretics**: 'water pills' – e.g. furosemide, bendroflumethiazide, indapamide, bumetanide

Diabetes Medication Sick Day Rules

- When you are unwell with repeated vomiting or diarrhoea, or fever with sweats and shaking …STOP taking the medicines listed overleaf
- Contact your GP, pharmacist or named nurse
- You may need to carry out blood glucose and ketone checks and have a blood test in the lab organised by your GP
- Restart these medications when eating and drinking normally after 24-48 hours or as advised by your GP
- If on insulin seek medical advice regarding dose adjustment if uncertain - but never stop insulin

Key messages

- The use of SGLT-2 inhibitors is associated with a small but increased risk of diabetic ketoacidosis in both type 1 and type 2 diabetes
- Caution should be exercised when using SGLT-2 inhibitors in patients who are at high risk of ketoacidosis due to other reasons like dehydration, stress, admission into hospital for elective surgery, trauma, acute medical illness or any other catabolic state
- Blood glucose levels may not be elevated in SGLT-2 inhibitor associated ketoacidosis and the diagnosis can be missed
- Treatment of SGLT-2 inhibitor associated ketoacidosis may require a variable, rather than a fixed, rate intravenous insulin infusion and intravenous dextrose to prevent hypoglycaemia
- The use of SGLT-2 inhibitors in type 1 diabetes, outside of clinical trials, is not recommended
- Local systems and prompts should be introduced to warn both patients and health care professionals about the risk of SGLT-2 inhibitor associated ketoacidosis

and other medication which might potentially cause harm during acute illness (Figure 1).

5. Avoid excess alcohol intake and very low calorie diets when taking SGLT-2 inhibitors.
6. When SGLT-2 inhibitors are used glucose levels may drop triggering a reduction in insulin dose which should be monitored carefully as insulin deficiency may precipitate ketosis and subsequent acidosis in patients who are relatively insulin deficient.
7. In patients taking SGLT-2 inhibitors, if there are any symptoms suggestive of diabetic ketoacidosis for example vomiting and abdominal pain, blood ketones should be measured in addition to urinary ketones. Urinary ketones may be negative because of increased ketone resorption and plasma glucose may not be particularly high. As patients with type 2 diabetes may not have meters to test blood ketones, they may have to visit their GP or nearest hospital for blood ketone testing.
8. ABCD strongly emphasises that SGLT-2 inhibitors are not currently approved for use in type 1 diabetes. However, if these are used off-label or in clinical trials, insulin dose should not be reduced in response to a reduction in blood glucose levels without careful consideration of the risk of ketoacidosis and ketone monitoring.
9. ABCD strongly advise that patients with type 1 diabetes prescribed an SGLT-2 inhibitor should give informed consent that makes them fully aware of the potential for euglycaemic diabetic ketoacidosis (euDKA), the precipitating factors, the warning symptoms and signs and the preventive measures to adopt.[23,39] Written advice and guidance should be provided for these patients.
10. In patients taking insulin who are being treated as having type 2 diabetes similar considerations should apply before reducing insulin dose and as insulin dose is reduced.

Overall recommendations

DKA occurs infrequently in patients with type 2 diabetes taking SGLT-2 inhibitors and ABCD believes that the risk-benefit ratio currently overwhelmingly favours continuing the current practice of using SGLT-2 inhibitors with no change in current recommendations as long as their use is within licensed indications.

There should, however, be provision for education, training guidelines and prompts in clinical systems to warn clinicians that the diagnosis of DKA may be missed in patients prescribed SGLT-2 inhibitors because of lower than anticipated glucose levels. The diagnosis of DKA should be considered when patients from high risk groups and with high risk conditions present with acidosis or symptoms compatible with acidosis.

The potential benefit of using SGLT-2 inhibitors in addition to insulin in type 1 diabetes is a reduction in insulin dose and less weight gain. The risk of DKA is higher in these patients but can possibly be mitigated by using a lower SGLT-2 dose, avoiding sharp reductions in insulin dose and regular monitoring of ketones particularly in high risk situations.

The above recommendations should also be considered in patients with type 2 diabetes taking SGLT- 2 inhibitors particularly in those patients likely to have low beta cell reserve.

Conclusions

In general, the rate and prevalence of DKA in people with type 2 diabetes taking SGLT-2 inhibitors is very low and does not warrant a change in practice in the use of these agents.

In patients with type 1 diabetes or insulin treated type 2 diabetes it would make pragmatic sense to anticipate and monitor for possible DKA in situations which are known to precipitate metabolic decompensation (injury, infections, stressful events and catabolic states).

There should be prompts to identify patients attending Emergency Departments or Medical Admissions Units who are prescribed SGLT-2 inhibitors to warn of the possibility of euDKA. SGLT-2 inhibitors should be discontinued in patients who have developed DKA and should not be restarted unless a clear alternative cause of DKA is identified.

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