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Title	SGLT2 inhibitors: managing the small but critical risk of diabetic ketoacidosis
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Sodium–glucose cotransporter type 2 inhibitors: managing the small but critical risk of diabetic ketoacidosis

Risk of SGLT2 inhibitor-associated diabetic ketoacidosis in type 2 diabetes: some answers, but more questions

Prescribers have enthusiastically embraced sodium–glucose cotransporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes on the strength of accumulating data reporting improved cardiovascular and renal outcomes. In Australia, in 2016, 757 826 Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme prescriptions containing an SGLT2 inhibitor were dispensed. By 2019, that number had risen to 2.3 million.¹ Assuming these scripts are dispensed monthly, an estimated 19% of all patients with type 2 diabetes (about 190 000 people) are currently being treated with SGLT2 inhibitors.

Cardiovascular and renal benefits

Landmark cardiovascular outcome trials of SGLT2 inhibitors in patients with type 2 diabetes and high cardiovascular risk have reported reduced all-cause mortality with empagliflozin,² reduced cardiovascular death with empagliflozin and dapagliflozin,^{2,3} and reduced hospitalisation for heart failure with empagliflozin, dapagliflozin and canagliflozin.^{2–4} These outcomes appear independent of the glucose-lowering effect of SGLT2 inhibitors, which results in a modest 0.7% reduction in glycated haemoglobin (HbA_{1c}) levels, similar to other oral hypoglycaemic agents. Of considerable interest is the recent DAPA-HF trial,⁵ which examined the effects of dapagliflozin versus placebo in patients with and without diabetes who had a left ventricular ejection fraction of 40% or less. The primary outcome of cardiovascular death or worsening heart failure in the dapagliflozin group was reduced (hazard ratio, 0.74; 95% CI, 0.65–0.85; $P < 0.001$; number needed to treat = 21), and the benefits were the same irrespective of diabetes status.⁵ There is also increasing evidence for beneficial renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes. In the CREDENCE trial,⁶ canagliflozin reduced the relative risk of the primary outcome of end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular disease by 30%.⁶ These findings are consistent with the beneficial secondary renal outcomes observed in the

EMPA-REG (empagliflozin)⁷ and DECLARE-TIMI 58 (dapagliflozin) trials.⁸ It is notable that in EMPA-REG and CREDENCE, 7.7% and 27.2% of patients respectively had an estimated glomerular filtration rate (eGFR) value below 45 mL/min/1.73m². At these eGFR levels, the glycosuric effect of SGLT2 inhibitors is markedly diminished, suggesting that renal benefits are unrelated to blood glucose improvement. The product information approved by the Therapeutic Goods Administration (TGA), which is based on the hypoglycaemic effects of these drugs, currently sets an eGFR lower limit of 45–60 mL/min/1.73m², depending on the SGLT2 inhibitor used, but this may change as new data accrue.

Adverse effects

In general, these drugs are well tolerated. Genital candidiasis occurs more commonly in SGLT2 inhibitor users and may lead to discontinuation. Severe necrotising fasciitis of the perineum (Fournier's gangrene) has rarely been reported in men and women. An uncommon but important adverse effect is diabetic ketoacidosis (DKA).

SGLT2 inhibitors increase ketogenesis

SGLT2 inhibitors have multiple mechanisms of action. First, they reduce plasma glucose concentrations by blocking the SGLT2 transporter in the proximal renal tubule with resultant glycosuria. Second, they improve insulin sensitivity and possibly β -cell function. Third, SGLT2 inhibitors stimulate glucagon secretion. This latter effect is important because an elevation in the glucagon to insulin ratio predisposes to increased lipolysis and ketogenesis — a metabolic pathway that underpins the known risk of DKA in users of SGLT2 inhibitors. In addition, SGLT2 inhibitors decrease renal clearance of ketones especially in states of dehydration.

Diabetic ketoacidosis risk

In patients with type 2 diabetes, SGLT2 inhibitor users have a 50–100% increase in relative risk of DKA.^{3,9} In our recent study, the absolute risk of DKA was small, being 1.02 per 1000 (95% CI, 0.74–1.41 per 1000) in SGLT2 inhibitor users versus 0.69 per 1000 (95% CI, 0.58–0.82 per 1000) in non-SGLT2 inhibitor users (odds ratio [OR], 1.48; 95% CI, 1.02–2.15; $P = 0.037$) over a 26-month period.⁹ However, the risk of developing DKA as an inpatient was significantly higher in SGLT2 inhibitor users than in non-users (OR, 37.4; 95% CI, 8.0–175.9; $P < 0.0001$).⁹ Notably, blood glucose levels may be normal or only slightly elevated in SGLT2 inhibitor-associated DKA, giving rise to the term “euglycaemic DKA”, which may lead to delays in diagnosis and treatment. In the DAPA-HF trial, DKA was observed in 0.1% ($n = 3$) of the subjects treated with dapagliflozin and in none of the patients allocated to the placebo group, DKA cases only occurred in patients with diabetes.⁵

Blood ketone concentrations are elevated in physiological states; for example, when

fasting, after exercise, during pregnancy, in the neonate, and in pathological states such as DKA. After an overnight fast in non-diabetic individuals, blood ketones are typically less than 0.6 mmol/L, rising to 1.0 mmol/L during prolonged fasting for 16–20 hours,¹⁰ while DKA in patients with type 1 diabetes is usually associated with blood ketones of 3.0–20.0 mmol/L.

The recognition of SGLT2 inhibitor-associated DKA has led to guidelines from the Australian Diabetes Society and the Australian and New Zealand College of Anaesthetists that appropriately advise withholding these drugs (except for minor procedures with a short period of fasting, no dehydration and rapid resumption of eating) for 2 full days before surgery and on the day of surgery and also at times of medical illness associated with reduced oral intake.^{11,12}

Current issues

There are practical issues regarding the advice to withhold SGLT2 inhibitors before surgery. First, the merit of testing blood ketones before procedures is not evidence-based and is uncertain. We are aware of several local cases in which well patients underwent colonoscopy preparation, withheld their SGLT2 inhibitors for 3 days as instructed, but were then cancelled on the day of the planned procedure because their blood ketones were just above 1.5 mmol/L (with normal plasma bicarbonate and normal plasma glucose). While our study showed no cases of DKA associated with colonoscopy, gastroscopy or coronary angiography,⁹ a TGA enquiry revealed that four of 319 SGLT2 inhibitor-associated DKA reports were linked to colonoscopy in patients with type 2 diabetes.¹³ None were associated with gastroscopy or coronary angiography. It seems prudent to withhold SGLT2 inhibitors before colonoscopy but not necessarily for other routine day procedures for which minimal fasting is required.

Variable blood ketone concentrations ranging from 0.2 mmol/L to more than 0.67 mmol/L have been reported in fasting, well patients taking SGLT2 inhibitors.^{14,15} One study concluded that transient ketosis without symptoms or signs of acidosis was not infrequent in SGLT2 inhibitor users, even with relatively well controlled type 2 diabetes.¹⁶ Data are lacking regarding the expected concentrations of blood ketones in fasted patients who have recently ceased SGLT2 inhibitors. In light of the variable degree of ketonaemia reported in users of SGLT2 inhibitors, better evidence is required about the threshold of serum ketones that comprise a clinically significant risk for DKA in patients who are fasting for elective procedures. When patients have ceased the SGLT2 inhibitors for 3 days before a procedure, we suggest that blood ketones should only be checked if the patient is clinically unwell or develops nausea and/or vomiting. While we must take seriously the periprocedure risk of SGLT2 inhibitor-associated DKA, we should also not overreact to blood ketone levels when they are tested.

In patients who have continued using SGLT2 inhibitors before an operation, we agree with the recently updated Australian Diabetes Society's guideline advice to consider surgery postponement if blood ketones are greater than 1.0 mmol/L and venous pH is

below 7.3, but surgery could proceed when blood ketones are greater than 1.0 mmol/L if the venous pH is 7.3 or greater and the HbA_{1c} level is below 75 mmol/mol (9.0%).¹² Intravenous insulin–dextrose infusion should be used in the latter cases to treat the ketosis and prevent progression to ketoacidosis.¹²

Second, what is the optimal management of patients who are admitted for urgent surgery and are currently taking SGLT2 inhibitors? There are no clinical studies to guide us, but surgery should proceed, with vigilance for the possible development of euglycaemic DKA after the operation. In this situation, blood ketones should be monitored hourly during the procedure and then every 2 hours until the patient is eating normally. Plasma bicarbonate should be checked if blood ketones rise above 1.0 mmol/L. It is essential to be aware that a normal or modestly elevated blood glucose level does not exclude DKA.

Third, what should be done for patients who are taking an SGLT2 inhibitor in a fixed-dose combination tablet (with metformin or a dipeptidyl peptidase 4 [DPP4] inhibitor)? How do we minimise the risk of elective surgery being cancelled because a patient stops their fixed-dose tablet and presents with hyperglycaemia? A somewhat cumbersome solution is to provide the patient with a prescription for only 2 days' supply of the non-SGLT2 inhibitor component of the fixed-dose combination. A better solution would be for the relevant pharmaceutical companies to supply general practitioners and hospital pharmacies with complimentary 2-day packs containing either metformin or DPP4-inhibitor, analogous to the starter packs that are made available when a patient starts taking a new drug.

Fourth, there remain a number of practical questions. How should patients, who often have multiple comorbidities, be warned of the symptoms of euglycaemic DKA (Box)? How do we present the information in a way that does not cause excessive anxiety, so that patients are not fearful about taking the SGLT2 inhibitors? Abdominal pain, nausea or vomiting should generally prompt a diagnostic check for DKA. However, nausea is a common symptom; so when should a patient seek urgent medical attention? Should all SGLT2 inhibitor-treated patients have a home meter capable of testing blood ketones? If so, how should the meters and ketone strips be funded?

Conclusion

SGLT2 inhibitors are important drugs with a number of benefits. The small but critical risk of DKA can be managed with appropriate patient and clinician action.

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[Insert Box]

Guidelines for managing the risk of diabetic ketoacidosis (DKA) in patients taking sodium–glucose cotransporter type 2 (SGLT2) inhibitors (*National Health and Medical Research Council Grade C recommendation*)¹⁷

Location of care	SGLT2 inhibitor use	Action*
Community [†]	Initiation and then every 6–12 months	<ul style="list-style-type: none"> ▪ Discuss the small risk of DKA, advising that potential benefits far outweigh the risk ▪ Advise patient (verbally and in writing) to seek urgent medical attention if nausea, vomiting, abdominal pain, malaise, or rapid breathing occur, as these may be signs of DKA ▪ Advise patient (verbally and in writing) to temporarily stop SGLT2 inhibitors if unwell with an intercurrent illness or if they are not eating normally ▪ Advise patient to avoid low carbohydrate (ketogenic) diets while taking SGLT2 inhibitors
Community/hospital	Initiation and then every 6–12 months	<ul style="list-style-type: none"> ▪ Advise patient (verbally and in writing) to stop SGLT2 inhibitors 2 full days before and the day of elective surgery and colonoscopy. Cessation is usually not required for same-day surgery, coronary angiography or gastroscopy ▪ For patients taking a fixed-dose combination SGLT2 inhibitors and metformin[‡] or SGLT2 inhibitors and DPP4 inhibitors,[§] prescribe the metformin or DPP4 inhibitor separately to cover the 2 days when the SGLT2 inhibitor is withheld. Short term, insulin therapy may be required in some cases
	At any time	<ul style="list-style-type: none"> ▪ Check blood ketones and venous bicarbonate urgently in any unwell patient who is taking SGLT2 inhibitors. Normal or only minor elevations of blood glucose may occur in SGLT2 inhibitor-associated DKA
Hospital	At any time [¶]	<ul style="list-style-type: none"> ▪ Withhold SGLT2 inhibitors until the patient is eating normally after surgery ▪ Withhold SGLT2 inhibitors if a patient is unwell with a medical illness until they are eating normally
	If the patient has not stopped SGLT2 inhibitors at least 2 full days before the operation [¶]	<ul style="list-style-type: none"> ▪ Defer all non-urgent surgery if HbA_{1c} > 75 mmol/mol (9.0%) ▪ Non-urgent surgery can proceed if: <ul style="list-style-type: none"> ▶ HbA_{1c} ≤ 75 mmol/mol (9.0%), blood ketones ≤ 1.0 mmol/L (monitor blood ketones hourly during the procedure and every 2 hours after the procedure until eating and drinking normally); ▶ HbA_{1c} ≤ 75 mmol/mol (9.0%), blood ketones > 1.0 mmol/L and venous pH ≥ 7.30. The elevated ketones may reflect starvation ketosis combined with the effect of SGLT2 inhibitors. Manage with intravenous insulin–dextrose infusion to treat the ketosis and prevent progression to ketoacidosis (monitor blood ketones hourly during the procedure and every 2 hours after the procedure until eating and drinking normally) ▪ Urgent surgery: <ul style="list-style-type: none"> ▶ monitor blood ketones hourly during the procedure and every 2 hours after the procedure until eating and drinking normally;

► if the blood ketone level is > 1.0 mmol/L, a venous blood gases test should be done urgently to measure pH. If pH < 7.30, manage with insulin–dextrose infusion

DPP4 = dipeptidyl peptidase 4; HbA_{1c} = glycated haemoglobin. * Advice should be given by the prescriber but may also be given by a pharmacist or diabetes educator. † Community refers mainly to general practice but also includes hospital outpatient clinics. Initiation may also occur in the inpatient setting; ‡ Currently available brands of fixed combination SGLT2 inhibitors and metformin: Xigduo XR (AstraZeneca), Jardiamet (Boehringer Ingelheim), Segluromet (Merck Sharp and Dohme, Australia). § Currently available Pharmaceutical Benefits Scheme brands of fixed-dose combination SGLT2 and DPP4 inhibitors: Glyxambi (Boehringer Ingelheim), Qtern (AstraZeneca), Steglujan (Merck Sharp and Dohme, Australia). ¶ Adapted from the Australian Diabetes Society.¹²

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