

ALERT UPDATE May 2023

Periprocedural Diabetic Ketoacidosis (DKA) with SGLT2 Inhibitor Use In People with Diabetes

Background

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are oral medications that promote glucose excretion in the urine for the treatment of type 2 diabetes. Note that SGLT2i are not approved for use in the management of type 1 diabetes in Australia or New Zealand, although they are sometimes used off-label in this setting.

- Over the last few years there has been an increasing number of reports of people with type 2 diabetes who are taking these medications developing severe acidosis requiring ICU/HDU admission during the peri-operative period.
- SGLT2i carry a small but definite risk of severe diabetic ketoacidosis (DKA), which may be associated with near-normal or only mildly elevated blood glucose levels (i.e. 'euglycaemic' ketoacidosis [euDKA]); therefore, a normal or only modestly elevated plasma glucose level does not exclude the diagnosis.
- The risk is increased if the person with diabetes has been fasting or has very restricted dietary (especially carbohydrate) intake, has undergone bowel preparation and/or a surgical procedure, is dehydrated or has an intercurrent illness such as active infection.
- Blood ketone testing is strongly recommended to detect and monitor DKA as urine ketone testing may be unreliable.
- It should be noted that ketone levels may be elevated in a person with diabetes undergoing colonoscopy due to the decreased carbohydrate intake during the preparation for colonoscopy, even in people who are not administered SGLT2i. In people with and without type 2 diabetes and not taking SGLT2i, ketone levels up to 1.7 mmol/L have been reported in the absence of acidosis.

Clinicians should consider DKA/euDKA in a person with diabetes taking SGLT2i who has one or more of:

- Symptoms of abdominal pain, nausea, vomiting, fatigue or metabolic acidosis
- Finger prick capillary blood ketone (or blood beta-hydroxybutyrate) levels >1.0 mmol/L with or without hyperglycaemia
- Low (negative) base excess (BE) <-5 mmol/L indicating metabolic acidosis on arterial or venous blood gasses.

SGLT2i agents currently available in Australia include dapagliflozin (Forxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro), as well as fixed dose combinations with metformin (Xigduo, Jardiamet, Segluromet) or with gliptins (Glyxambi, Qtern, Steglujan).

SGLT2i agents currently registered in New Zealand include dapagliflozin (Forxiga), empagliflozin (Jardiance) and canagliflozin (Invokana). N.B. only dapagliflozin (Forxiga) and empagliflozin (Jardiance) are currently commercially available.

Advice for peri-procedural practice

- When commencing a person with diabetes on SGLT2i, clinicians should inform them about the risk of DKA associated with procedures, ideally with written information and management plans. It is advisable to document that the advice has been provided.
- For surgery and procedures requiring one or more days in hospital, omit SGLT2i for at least 3 days (i.e. 2 days pre-procedure, and the day of procedure). This may require increasing other glucose-lowering drugs during that time. If the SGLT2i is part of a fixed dose combination, this will lead to withdrawal of two glucose-lowering drugs unless the second drug is prescribed separately.
- For surgery and procedures including colonoscopy requiring bowel preparation with carbohydrate restriction commencing on the day prior to the procedure, omit SGLT2i for at least 3 days (i.e. 2 days pre-procedure, and the day of procedure).
- For day-stay procedures (including gastroscopy) that do not require bowel preparation, SGLT2i can be stopped just for the day of procedure. However, fasting before and after the procedure should be minimised.

On admission

- If the person with diabetes is unwell: strongly consider postponing non-urgent procedures.
- Measure both blood glucose and blood ketone levels. If the person with diabetes has ceased the SGLT2i 3 days pre-procedure, is clinically well and ketones are < 1.7 mmol/L, proceed. Consider hourly blood glucose and blood ketone testing during the procedure and 2 hourly following the procedure until the person with diabetes is eating and drinking normally.
- If the SGLT2i has not been omitted for 3 days (i.e. 2 days prior to surgery and the day of surgery) or if the SGLT2i has been taken on the day of surgery or the day procedure, the course of action depends on the urgency of the procedure, comorbidities of the person with diabetes, surgical factors, HbA1c, blood ketones, and base-excess (see table). *Note HbA1c >9% or 75 mmol/mol is an indicator of insulin insufficiency. It confers a higher risk of DKA in this setting.*
- A person with diabetes on SGLT2i undergoing emergency surgery should be admitted post-procedure to a ward capable of managing diabetic ketoacidosis in collaboration with endocrinology and critical care.
- **At any point before, during or after a procedure, if the blood ketone level is >1.0 mmol/L in an unwell person with diabetes** who has been on an SGLT2i, take arterial or venous blood gases to measure the (standard) Base Excess (SBE). If ketones are > 1.0 mmol/L and base excess <-5 mmol/L, the person with diabetes has presumed DKA, and if the blood glucose < 14 mmol/L, presumed euDKA.
 - For the person with diabetes in a ward, or where there is no critical care expert, the rapid response (MET) team should be activated or an ICU contacted, and collaboration sought with endocrinology or general medicine.
 - In other critical care areas, anaesthetists or emergency medicine physicians should liaise with endocrinology and ICU. Management priorities include: rehydration; intravenous insulin (with added glucose infusion if the BGL is <15mmol/l); hourly monitoring of blood glucose, ketones and blood gases with appropriate action to escalate or de-escalate treatment.
- A person with diabetes with DKA and euDKA should be reviewed by an endocrinologist or physician on-call and critical care specialists. If required, contact a tertiary hospital for expert advice.

Post procedure

- Restart SGLT2i post-operatively when the person with diabetes is eating and drinking normally or close to discharge from hospital.
- A person with diabetes who has day surgery/procedures should only recommence SGLT2i when they resume full oral intake. Consider delaying recommencement of SGLT2i for a further 24 hours but also consider potential for hyperglycaemia.
- Provide the person with diabetes with written advice to seek medical advice if unwell in the week following the procedure.

Table: Suggested Management of CLINICALLY WELL a person with diabetes who has NOT ceased SGLT2i

Ketones	Base Excess	Comments
<1	> -5	No ketosis and no metabolic acidosis. Consider proceeding with day surgery: hourly monitoring of blood ketones during the procedure, and 2 nd hourly following the procedure until eating and drinking normally or discharged. Where blood gas analysis is not available proceed only if added risk is consistent with goals of care. More extensive surgery: consider goals of care and collaboration with endocrinology and critical care. Perioperative insulin and glucose infusion may reduce risk.
>1	> -5	Ketosis without metabolic acidosis. Seek endocrinology or general medicine advice. Ketosis without acidosis may reflect starvation, particularly in individuals with HbA1c < 9% (<75 mmol/mol). Consider proceeding, but with perioperative insulin and glucose infusion to reduce risk of ketoacidosis
>1	< -5	Ketosis with metabolic acidosis. Postpone non-urgent surgery. Escalate care with endocrinology and critical care. Urgent surgery to proceed with insulin and glucose infusion and ketone monitoring with guidance from endocrinology and/or critical care

Footnote: Blood gas analysis is recommended to assess for presence of metabolic acidosis. Where blood gas analysis is not readily available, and the ketones are > 1.0 mmol/L the procedure should not be performed.

Precaution:

This updated management alert on the use of SGLT2 inhibitors in relation to periprocedural DKA risk should not supplant individualised clinical decisions based on the circumstances of each clinical scenario.

Resources

1. Hamblin PS, Wong R, Ekinci EI, Furlanos S et al. SGLT2 Inhibitors Increase the Risk of Diabetic Ketoacidosis Developing in the Community and During Hospital Admission. *J Clin Endocrinol Metab* 2019; 104: 3077-308.
2. Meyer EJ, Gabb G, Jesudason D. SGLT2 Inhibitor–Associated Euglycemic Diabetic Ketoacidosis: A South Australian Clinical Case Series and Australian Spontaneous Adverse Event Notifications. *Diabetes Care*. 2018; 41: e47-e49.
3. Peacock SC, Lovshin, JA Can J. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in the perioperative setting. *Anesth/J Can Anesth*. 2018; 65:143–147.
4. Thiruvankatarajan V, Meyer EJ, Nanjappa N, Van Wijk RM, Jesudason D. Perioperative diabetic ketoacidosis with sodium-glucose co-transporter-2 inhibitors: a systematic review. *Br J Anaesth* 2019; 123:27-36.
5. Isaacs M, Tonks KT, Greenfield JR. Euglycaemic diabetic ketoacidosis in patients using sodium-glucose co-transporter 2 inhibitors. *Intern Med J* 2017; 47:701-704.
6. Fralick M, Schneeweiss S, Paterno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. *N Engl J Medicine*. 2017; 376:2300–2302.
7. Peters AL, Henry RR, Thakkar P, Tong C, Alba M. Diabetic ketoacidosis with canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. *Diabetes Care*. 2016; 39:532-538.
8. <https://www.tga.gov.au/alert/sodium-glucose-co-transporter-2-inhibitors> 18 July 2018
9. European Medicines Agency. Review of diabetes medicines called SGLT2 inhibitors started: risk of diabetic ketoacidosis to Base-Excess examined [Internet], 12 June 2015. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors/20/Procedure_started/WC_50_01_87_92_6.pdf.
10. AACE/ACE Position Statement American Association Of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of SGLT-2 Inhibitors And Diabetic Ketoacidosis. *Endocrine Practice*: 2016; 226:753-762.
11. Danne T, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors. *Diabetes Care*. 2019; 42:1147-1154
12. Meyer EJ, Mignone E, Hade A, Thiruvankatarajan V, Bryant RV, Jesudason D. Periprocedural euglycemic ketoacidosis associated with sodium-glucose cotransporter 2 inhibitor therapy during colonoscopy. *Diabetes Care*. 2020; 43:e181-e184.
13. Hamblin S, Wong R, Ekinci EI, Sztal-Mazer S, et al. Capillary ketone concentrations at the time of colonoscopy: a cross-sectional study with implications for SGLT2 inhibitor-treated type 2 diabetes. *Diabetes Care* 2021; 44:e1-e3.