



Type 2 Diabetes: SGLT2 Inhibitors and Diabetic Ketoacidosis

B.C. Provincial Academic Detailing Service

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Health Canada, the US Food and Drug Administration, and the European Medicines Agency have issued warnings that SGLT2 inhibitors increase the risk of diabetic ketoacidosis (DKA).¹⁻³

The first SGLT2 inhibitor (SGLT2i) was approved by Health Canada in 2014. The class now includes: **canagliflozin, empagliflozin, dapagliflozin and ertugliflozin**. An August 2019 search of Health Canada's Drug and Health Product Register for these agents identifies approximately 600 adverse reaction reports in which the term 'acidosis' occurs.⁴ Large randomized controlled trials (RCTs) of SGLT2 inhibitors demonstrate an increased risk of DKA.⁵

- In cardiovascular outcome trials, the risk is two times higher in people randomized to an SGLT2i compared to placebo (HR 2.20, 95%CI 1.25 to 3.87): DKA event rates < 1 per 1000 patient years.⁵
- In a 2019 RCT of patients with diabetic nephropathy, the risk was increased approximately 10 fold with canagliflozin compared to placebo (HR 10.8, 95%CI 1.39 to 83.65): DKA event rate 2.2 per 1000 patient years.⁶

Predisposing and/or precipitating factors for SGLT2 inhibitor DKA may include:^{1-3,7}

- Pancreatic disorders causing insulin deficiency (e.g. type 1 diabetes, pancreatitis, pancreatic surgery)
- Long-standing type 2 diabetes / latent autoimmune diabetes in adults
- Sudden reduction or omission of insulin dose
- Acute serious illness / infection / acute febrile illness
- Major surgery / hospitalization
- Reduced caloric intake / low carbohydrate diet / intensive exercise
- High alcohol consumption

SGLT2 inhibitor DKA may occur with lower-than-anticipated blood glucose values.^{1-3,8}

DKA is often accompanied by glucose levels greater than 14 mmol/L, however DKA with lower-than-anticipated glucose levels has been reported in young individuals with type 1 diabetes, pregnant women, and more recently, in individuals receiving SGLT2 inhibitor therapy.⁸ **DKA should be suspected** in individuals prescribed an SGLT2i who present with DKA symptoms (Table 1), **despite normal or near-normal glucose values**.⁸

Patients and clinicians should be aware of the signs and symptoms of DKA.

Educate patients that they should seek medical attention based on their symptoms (Table 1), rather than their blood glucose levels.¹⁰ Patients should also receive **clear instructions** on when to withhold their SGLT2 inhibitor in the case of illness or surgery, and when it can be restarted (Table 2).

DKA is a **medical emergency** requiring prompt treatment and immediate discontinuation of the SGLT2i with assessment of the appropriateness of re-initiation after recovery.^{3,11} Note that the glycosuric effects of SGLT2i can persist for at least a few days after discontinuation.^{7,8}

Table 1: Possible Symptoms of DKA^{7,9}

fast deep breathing / feeling short of breath
nausea or vomiting / stomach pain
loss of appetite / excessive thirst
unusual sleepiness or tiredness
confusion / slurred speech
rapid heart rate

Strategies aimed at addressing the risk of DKA have been proposed.

Table 2: Proposed strategies to address the risk of DKA^{2,3,8,10,12}

Acute Serious Illness	<ul style="list-style-type: none"> ▪ hold SGLT2i at onset of illness ▪ restart when feeling well and able to eat and drink
Major Surgery	<ul style="list-style-type: none"> ▪ hold 3 days before surgery ▪ restart after acute phase response and physiological stress has resolved, and is feeling well and able to eat and drink
Bariatric Surgery	<ul style="list-style-type: none"> ▪ hold SGLT2i during preoperative low-carbohydrate diet ▪ reassess postoperatively
Low Intake of Carbohydrates	<ul style="list-style-type: none"> ▪ hold until normal diet resumes
Excess Intake of Alcohol	<ul style="list-style-type: none"> ▪ stop immediately ▪ reassess at later date

References

1. Summary Safety Review - SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin) - Assessing the Risk of the Body Producing High Levels of Acids in the Blood (diabetic ketoacidosis) <https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?linkID=SSR00013>
2. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about>
3. EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes <https://www.ema.europa.eu/en/medicines/human/referrals/sglt2-inhibitors>
4. Government of Canada. Drug Product Database. [Internet]. <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>. Accessed August 14, 2019.
5. Zelniker TA et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*. 2019; 393(10166):31-39
6. Perkovic V et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *NEJM*. 2019; DOI: 10.1056/NEJMoa1811744
7. Handelsman Y et al. 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;22(6):753-762
8. Goldenberg RM et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. *J Clin Thera* 2016. <http://dx.doi.org/10.1016/j.clinthera.2016.11.002>
9. Goguen J, Gilbert J. Hyperglycemic Emergencies in Adults: 2018 Clinical Practice Guidelines. *Can J Diabetes* 2018. <https://doi.org/10.1016/j.cjcd.2017.10.013>
10. Zhang L, Tamilia M. Euglycemic diabetic ketoacidosis associated with the use of a sodium-glucose cotransporter-2 inhibitor. *CMAJ* 2018;190:E766-8. doi: 10.1503/cmaj.171319
11. Gosmanov AR, Wall Barry M. Diabetic Ketoacidosis. *Conn's Current Therapy* 2019. DOI:10.1016/B978-0-323-59648-0.00066-3
12. Kerridge R et al. The good, the bad, and the ugly: sodium-glucose cotransporter-2 inhibitors (gliflozins) and perioperative diabetes. *Anaesth Intensive Care* 2018; 46(2):155-158