

Diabetes SGLT2 inhibitors

Evidence check

17 November 2021

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Evidence check questions

Q1. What is the evidence on the safety of the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors in an inpatient setting for people with diabetes?

Q2. Are there any existing recommendations in the literature regarding the use of SGLT2 inhibitors in an inpatient setting for people with diabetes?

In brief

- SGLT2 inhibitors (SGLT2-i) (also known as gliflozins) are anti-hyperglycaemic agents that alter the physiology of the nephron, preventing the kidneys from reabsorbing glucose into the blood.¹⁻³ They are generally used in conjunction with diet, exercise and other oral hypoglycaemics or insulin.²
- Treatment with SGLT2-i has been associated with diabetic ketoacidosis (DKA), including euglycaemic ketoacidosis (atypical DKA that occurs at lower levels of blood glucose).⁴

Evidence on the safety of the use of SGLT2 inhibitors in an inpatient setting

- Surgery (elective or emergency) or procedures which require bowel preparation or modified diet, such as colonoscopy, are often identified as one of the predisposing conditions that are associated with DKA in patients using SGLT2-i medications.^{2, 3, 5-10}
 - Two systematic reviews found that withholding the use of SGLT2-i medications for less than 48 hours peri-operatively was one of the predisposing factors for developing euglycaemic DKA.^{9, 10}
 - In one recent case series study involving 23 patients who used SGLT2-i in the 48 hours before an emergency or elective surgery, 87% (n=20) developed ketosis, including 30% (n=7) who developed mild or moderate DKA.⁵
 - An analysis of spontaneous adverse event reports from the Australian Government Department of Health and Aged Care [Therapeutic Goods Administration](#) (TGA) found that 16% (53 out of 321) of the SGLT2-i-associated DKA cases occurred in the surgical setting.

- More cases occurred in the elective surgery setting than emergency setting (94.3% versus 5.7%).⁶
- SGLT2-i-associated DKA is more likely to occur postoperatively than preoperatively.⁶ One systematic review found that the time to postoperative DKA varied considerably, from one day to one month after the surgery.²
 - There are mixed findings on the benefits of and adverse events relating to the withdrawal of SGLT2-i medications.
 - One clinical audit study found no difference in the incidence rate of clinically detectable DKA in elective surgery patients who were admitted before and those who were admitted after the implementation of the protocolised preoperative cessation of the SGLT2-i medications; that is, no DKA was detected in either of the patient cohorts who withdrew SGLT2-i medications 24 hours or 72 hours before the surgery.¹¹
 - In one study, withholding SGLT2-i medications as per relevant guidelines was associated with:¹²
 - higher rates of postoperative complications (25% versus 7.58%, $p=0.04$), including euglycaemic DKA (6.25% versus 0%, $p=0.04$)
 - higher rates of urosepsis (18.75% versus 4.55%, $p=0.05$).
 - One systematic review found that there was no association between SGLT2-i cessation and the occurrence of DKA.¹³

Recommendations in the peer-reviewed literature

- Increasing awareness of euglycaemic DKA among clinicians³
- Developing local guidelines and appropriate communication strategies⁹
- Consideration of individual patient factors, the surgery type and the anticipated postoperative course that may increase the risk of DKA and influence preoperative planning²
 - Precipitating factors, other than surgical stress,¹⁴ that were mentioned in the literature include:
 - patients who were diagnosed with type 2 diabetes and were subsequently found to have latent autoimmune diabetes of adulthood¹⁰
 - changes to diabetes medication¹³
 - reduction in insulin dose^{8, 14} or discontinuation of insulin¹⁰
 - prolonged fasting^{8, 13}
 - low-calorie diet regimens^{13, 14}
 - alcohol use¹⁴
 - recent initiation of SGLT2-i medication¹⁴
 - infection^{8, 14}
 - intercurrent illnesses^{13, 14}
 - emergency surgery⁸
 - dehydration/hypovolaemia⁸
 - malignancy¹⁴
 - major trauma⁸
 - acute kidney injury⁸
 - delayed preoperative recognition of SGLT2-i use⁵
 - delayed recognition of ketosis⁵
 - administration of SGLT2-i close to surgery⁵
 - inadvertent preoperative administration of higher-than-recommended SGLT2-i doses⁵

- high-risk surgery such as bariatric or cardiothoracic^{2, 5, 6, 13}
 - gynaecologic or urologic surgery and/or usage of postoperative urinary catheters³
- A multidisciplinary approach involving the surgeon, anaesthetist and endocrinologist in planning appropriate blood glucose management and preventing DKA²
- Mixed recommendations for when the SGLT2-i should be withheld, including:
 - elective (or scheduled procedures):
 - the majority recommend 48 hours³ to 72 hours before surgery^{2, 8, 9}
 - one article recommends that for healthy short-stay patients or patients undergoing minor procedures such as day surgery: on the day of surgery¹³
 - other differential recommendations for minor procedures such as colonoscopy, state withdrawal two to three days prior²
 - emergency: as soon as possible⁸
 - patients whose resumption of oral intake is likely to be delayed, such as cardiac or abdominal surgery: a much longer duration¹³
 - bariatric procedures: two weeks before surgery²
- For patients who did not withhold SGLT2-i medications before elective or emergency surgery:
 - harm–benefit analysis of deferring the surgery^{3, 5}
 - closely monitoring blood glucose and for ketonaemia³
 - other mitigation strategies to prevent diabetic ketoacidosis^{5, 6}
- For patients who withheld SGLT2-i medications before elective or emergency surgery:
 - ensure adequate blood glucose control
 - perioperative insulin administration and better glycaemic control¹²
 - separately titrating drugs that are usually administered in combination with SGLT2-i medications while SGLT2-i medications are being withheld¹²
 - closely monitoring blood glucose and ketonaemia³
- It is often recommended that the SGLT2-i medications can be restarted once the patient is free from complications, euvolaemic, and eating and drinking normally^{2, 3, 8} or when the postoperative catabolic state is overcome by adequate oral intake¹³
- In high-risk patients, including patients undergoing bariatric surgery procedures, or if the SGLT2-i medications are recommenced soon after surgery:
 - close monitoring during the postoperative period.^{2, 8}
 - counselling patients about recognising suspicious symptoms
 - routine ketone checking⁸
- In patients who are likely to experience rapid weight loss, a low carbohydrate diet, or nausea/vomiting, indefinite suspension of the SGLT2-i medications may be considered.²

Recommendations in the grey literature

- The TGA recommends ceasing treatment with an SGLT2-i medicine before a major surgery.¹⁵
- The Australian Diabetes Society (ADS) and the New Zealand Society for the Study of Diabetes (NZSSD) recommend:¹⁶
 - cease SGLT2-i at least three days (two days before the procedure and the day of procedure) pre-procedure
 - if SGLT2-i has not been ceased three days prior or on the day, the course of action depends on the urgency of the surgery and patient factors
 - restart SGLT2-i medicine only when the patient is eating and drinking normally.

- The Food and Drug Administration (FDA) in the US recommends that canagliflozin, dapagliflozin and empagliflozin each should be stopped at least three days before, and ertugliflozin should be stopped at least four days before the scheduled surgery.¹⁷
- Other international guidelines recommend ceasing the use of SGLT2-i either 24 hours before the surgery or on the day of the surgery.¹⁸⁻²²

Limitations

Case report studies published before 2019 were not included as these were synthesised in systematic reviews that were included in this evidence check. Case reports with a small sample size (less than 10) were not included. Information relating to the clinical management of the SGLT2-i–associated DKA was neither extracted nor synthesised.

Background

SGLT2 inhibitors are one of the newest classes of drugs that are used for blood glucose control in patients with type 2 diabetes.³ The TGA advises that the risk of DKA with these drugs is increased in people who undergo surgical or medical procedures.¹⁵

Methods

Peer-reviewed articles were identified through PubMed. The search terms used are outlined in the [appendix](#). Grey literature search was conducted using Google.

Results

Table 1

Note: some of the information has been copied directly from the source material.

Source	Summary
Peer-reviewed sources	
<p>Metabolic outcomes in patients with diabetes mellitus administered SGLT2 inhibitors immediately before emergency or elective surgery: single centre experience and recommendations</p> <p>Wang et al. 2021⁵</p>	<ul style="list-style-type: none"> • Study design: case series study from Melbourne, Australia • Participants: 23 patients who used SGLT2-i (empagliflozin: n=15; dapagliflozin: n=8) in the 48 hours before emergency or elective surgery • Methods: statistical analysis of patient records • Results: 20 of 23 patients (87%) developed ketosis <ul style="list-style-type: none"> ○ 13 (57%) had ketosis without acidosis <ul style="list-style-type: none"> ▪ median ketosis duration was 16 hours (IQR:12-42) ○ 7 (30%) had DKA (mild, n=5; moderate, n=2; severe, n=0); 3 were euglycaemic at the time of peak ketosis <ul style="list-style-type: none"> ▪ median ketosis duration was 10 hours (IQR:8-75) ○ Median initial βOHb was 2.1mM (IQR: 0.7e3.6) ○ Median peak βOHb was 2.7mM (IQR: 1.2e4.6) ○ 15% (2 of 13) of patients recognised with ketosis before or during surgery developed DKA and 71% (5 of 7) patients recognised with ketosis after surgery developed DKA (p=0.02) ○ Risk factors for protracted ketoacidosis: <ul style="list-style-type: none"> ▪ delayed preoperative recognition of SGLT2-i use ▪ administration of SGLT2-i close to surgery ▪ inadvertent preoperative administration of higher-than-recommended SGLT2-i doses ▪ prolonged fasting, and high-risk surgery • Conclusion: For elective surgery patients who did not withhold SGLT2-i, risk–benefit analysis of deferring the surgery is recommended. For elective or emergency surgery patients, mitigation strategies to prevent DKA are recommended.
<p>Diabetic ketoacidosis in patients treated with SGLT2 inhibitors: experience at a tertiary hospital</p> <p>Papanastasiou et al. 2021²³</p>	<ul style="list-style-type: none"> • Study design: retrospective case cohort study from Greece • Participants: 6 patients with DKA due to SGLT2-i and 12 patients with DKA due to other causes • Methods: patient chart review • Results: compared with patients with DKA due to other causes, patients with SGLT2-i-induced DKA had: <ul style="list-style-type: none"> ○ lower glucose levels ○ similar HbA1c levels ○ similar severity of DKA ○ higher duration of insulin infusion ○ longer time required for DKA to resolve ○ increased fluid requirements ○ longer hospitalisation time

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	<ul style="list-style-type: none"> ○ similar total intravenous insulin and potassium administration until DKA resolution ● Conclusion: Patients with SGLT2-i–associated DKA had lower serum glucose levels on admission and required increased fluid administration and longer time to recover from acidosis compared to patients with DKA from other causes.
<p>An analysis of the Australian Therapeutic Goods Administration Database of Adverse Event Notifications of diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors in surgical patients</p> <p>Thiruvankatarajan et al. 2020⁶</p>	<ul style="list-style-type: none"> ● Study design: analysis of spontaneous adverse event reports from the TGA ● Participants: 321 SGLT2-i-associated DKA notifications ● Methods: a search of the TGA Database of Adverse Event Notifications (DAEN) for reports of SGLT2-i–associated DKA was undertaken up until October 2018. ● Results: of the 321 SGLT2-i–associated DKA notifications: <ul style="list-style-type: none"> ○ 53 (16%) occurred in the surgical setting: <ul style="list-style-type: none"> ▪ 3 were in the context of emergency surgeries ▪ 50 were presumed elective cases ▪ in 44 cases, where the specifics of surgery were known: <ul style="list-style-type: none"> ● 12 were cardiothoracic ● 6 were bariatric procedures ● of the 20 notifications which specified the type of diabetes, all were listed as type 2 diabetes ○ Time to presentation: available in 33 reports <ul style="list-style-type: none"> ▪ preoperatively (n = 2) ▪ during surgery (n = 2) ▪ up to three weeks postoperatively (n = 28) ● Conclusion: Until the true risk in surgical patients is defined, knowledge and vigilance are important to mitigate risk, especially as these SGLT2-i–associated DKA events are largely avoidable, particularly in the setting of elective surgery.
<p>The good, the bad, and the ugly: sodium-glucose cotransporter-2 inhibitors (gliflozins) and perioperative diabetes</p> <p>Kerridge et al. 2018³</p>	<p>This editorial proposes nine key recommendations for preoperative and postoperative care for people on SGLT2-i medications. The recommendations suggest slightly earlier preoperative cessation and emphasise that there should be no rush to recommence therapy postoperatively (refer to the paper for full recommendations).</p>
<p>Perioperative management of sodium-glucose cotransporter-2 inhibitors: importance of a nuanced approach.</p> <p>Nanjappa et al. 2018¹³</p>	<p>This correspondence questions the recommendation by Kerridge et al. that SGLT2-i should be withheld for a minimum of 72 hours preoperatively or even for 48 hours. The authors recommend a more nuanced approach, where it may be appropriate to withhold an SGLT2-i on the day of surgery and for 24 to 48 hours after surgery in a healthy patient who has access to blood ketone testing and is having a short day procedure, while a much longer duration of withholding SGLT2-i may be appropriate for significant abdominal or cardiac surgery, for example.</p>
<p>Management of sodium-glucose cotransporter 2 inhibitors during the perioperative period: A</p>	<ul style="list-style-type: none"> ● Study design: a retrospective comparative study ● Methods: 82 instances in 64 patients were included

<p>retrospective comparative study</p> <p>Ge et al. 2020¹²</p>	<ul style="list-style-type: none"> • Results: compared to instances where SGLT2-i medications were withheld per guidelines (n=66), instances where SGLT2-i medications were not withheld had: <ul style="list-style-type: none"> ○ higher postoperative complications (25% versus 7.58%, p=0.04) <ul style="list-style-type: none"> ▪ higher rates of euDKA (6.25% versus 0%, p=0.04) ▪ higher rates of urosepsis (18.75% versus 4.55%, p=0.05) ▪ higher rates of AKI (25% versus 7.58%, p=0.04) ○ similar rates of readmission within 28 days of surgery • Conclusion: Withholding SGLT2-i as per current guidelines was associated with an increase in postoperative complications and reduced glycaemic control.
<p>SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission</p> <p>Hamblin et al. 2019⁷</p>	<ul style="list-style-type: none"> • Study design: retrospective, multicentre, controlled cohort study • Participants: consecutive cases of DKA that developed in the community, or during the course of hospital admission, in patients with type 2 diabetes • Results: There were 162 cases of DKA (37 SGLT2-i users and 125 non-SGLT2-i users) with a physician-adjudicated diagnosis of type 2 diabetes. <ul style="list-style-type: none"> ○ DKA developed during the course of inpatient admission in 14 (38%) SGLT2-i users versus 2 (2%) non-SGLT2-i users (OR, 37.4; 95% CI: 8.0–175.9; P <0.0001). • Conclusion: SGLT2-i users were more likely to develop DKA as an inpatient compared with non-SGLT2-i users.
<p>The use of sodium-glucose co-transporter 2 inhibitors in the inpatient setting: Is the risk worth taking?</p> <p>Koufakis et al. 2020⁸</p>	<ul style="list-style-type: none"> • Study design: review • Methods: medical databases and clinical trial registries were searched. • Results: adverse events with focus on inpatient population and evidence related to the use of SGLT2-i in inpatient setting: <ul style="list-style-type: none"> ○ Precipitating factors: reduction in insulin dose, prolonged fasting, sepsis, emergency surgery, dehydration/hypovolaemia, major trauma, acute kidney injury ○ Main advantages of using SGLT2-i: <ul style="list-style-type: none"> ▪ low risk of hypoglycaemia ▪ practical dosing scheme ▪ potential to decrease heart failure admission rates ▪ optimal effects when administered in the acute phase of cardiovascular events (animal models) ○ Main disadvantages of use of SGLT2-i: <ul style="list-style-type: none"> ▪ increased risk of DKA ▪ increased risk of urinary tract infections ▪ increased risk of volume depletion ○ Precipitating factors of DKA are often met in hospitalised patients ○ Among surgical patients: <ul style="list-style-type: none"> ▪ The metabolic stress of surgery along with the need for prolonged fasting before and following major surgical procedures put surgical patients treated with SGLT2-i at high risk for developing DKA.

	<ul style="list-style-type: none"> ▪ Additional contributing factors to be considered are infections, dehydration due to diarrhoea or diuretics, severe trauma, omission of insulin or reduction in its dose and acute kidney injury. ▪ In case of scheduled procedures, the drug should be ideally discontinued 3 days before surgery ▪ In emergency procedures, the administration should be ceased as soon as possible. ▪ Postoperatively, treatment can start, provided that the patient is free of complications, euvolaemic and eats normally. <ul style="list-style-type: none"> • it would be preferable to withhold treatment with SGLT2-i during this time period. • in patients being at high risk for DKA, appropriate counselling should be given regarding the prompt recognition of suspicious symptoms, such as nausea and vomiting, and routine ketone checking might be recommended until re-evaluation. ▪ Individuals undergoing bariatric surgery procedures should be closely monitored during the first postoperative weeks. • Conclusion: Potential benefits derived from the use of SGLT2-i in the inpatient setting cannot mitigate possible risks, at least until robust evidence on the efficacy of SGLT2-i medications in hospitalised individuals becomes available.
<p>An audit of the effect of SGLT2 inhibitor cessation in a pre-admission clinic before and after Australian Diabetes Society guidelines</p> <p>Fookeerah et al. 2021¹¹</p>	<ul style="list-style-type: none"> • Study design: audit • Methods: compared perioperative outcomes in patients on SGLT2-i, before and after protocolised preoperative cessation of the drug. The protocol recommends: (i) suspending SGLT2-i therapy 72 hours before any type of surgery; (ii) measuring preoperative blood glucose and ketone levels; (iii) commencing i.v. insulin unless a short procedure is expected; and (iv) monitoring postoperative blood glucose and ketone levels for up to 3 days if normal oral intake is not resumed. • Results: There were no cases of clinically detected DKA in the 96 patients. • Conclusion: Withdrawal of SGLT2-i did not appear to alter significantly preoperative glycaemia. The incidence of clinically significant DKA associated with perioperative SGLT2-i use is low for patients undergoing elective surgery, if the medication is withheld for at least 24 hours before surgery. <p>34 (6.1%) patients in 2017 and 62 (11.4%) patients in 2019 were included.</p>
<p>Sodium-glucose cotransporter-2 inhibitors: an overview and perioperative implications</p> <p>Milder et al. 2018²</p>	<ul style="list-style-type: none"> • Study design: systematic review • Aim: to provide a critical appraisal of the pharmacology and safety profile of SGLT2-i, and to increase the awareness of perioperative physicians on SGLT2-i-associated euglycaemic DKA • Methods: 58 articles reporting SGLT2-i-associated ketoacidosis were included. • Results: major surgery is one of the predisposing factors for euglycaemic DKA with SGLT2-i.

	<ul style="list-style-type: none"> ○ 26 patients were identified where surgery was associated with ketoacidosis in those who were taking SGLT2-i: <ul style="list-style-type: none"> ▪ 19 of these were associated with canagliflozin. ▪ 20 of 26 patients had a plasma glucose level less than 14mmol.L-1. ▪ 8 patients had undergone bariatric procedures. These patients were placed on a low-carbohydrate, high-protein diet for one to two weeks preoperatively. ▪ The time at which ketoacidosis developed postoperatively varied considerably, from 1 day to 1 month post surgery. ▪ The SGLT2-i effect can persist for up to 10 days even in the presence of normal renal function, increasing the risk of recurrent ketoacidosis and perhaps suggesting that the pharmacodynamic effect may persist beyond five elimination half-lives. ○ Recommended prevention strategies include: <ul style="list-style-type: none"> ▪ Individual patient factors, the proposed surgery and the anticipated postoperative course should be taken into account. ▪ A multidisciplinary approach involving the surgeon, anaesthetist and endocrinologist is recommended. ▪ It may be appropriate to stop SGLT2-i approximately 3 days (or 5 half-lives) before major surgery. ▪ Some authors have recommended that SGLT2-i are ceased 1 week before elective surgery. ▪ For minor elective procedures that predispose the patient to a ketotic state (e.g. colonoscopies requiring bowel preparation and a modified diet), it is probably best if the SGLT2-i are stopped 2–3 days before the procedure. ▪ For bariatric procedures, SGLT2-i should be stopped 2 weeks before surgery. ▪ For emergency surgical cases, SGLT2-i should be stopped immediately. ▪ Post surgery, SGLT2-i should not be recommenced until the patient is clinically well, euvolaemic and tolerating a normal diet. ▪ If SGLT2-i is recommenced soon after surgery, the treating team must be vigilant and monitor for any symptoms of ketoacidosis (nausea, vomiting), which would mandate its immediate cessation. ▪ The risk of ketoacidosis is particularly high in the postoperative period due to rapid weight loss, a low-carbohydrate diet and nausea/vomiting. For these reasons it may be best if SGLT2-i is indefinitely suspended following surgery. ● Conclusion: The diagnosis of SGLT2-i–associated ketoacidosis may be delayed and it can be prevented by withholding SGLT2-i preoperatively and when indicated.
<p>Perioperative diabetic ketoacidosis associated with sodium-glucose co-</p>	<ul style="list-style-type: none"> ● Study design: systematic review ● Methods: reports of perioperative DKA involving SGLT2-i up to January 2019 were searched.

<p>transporter-2 inhibitors: a systematic review</p> <p>Thiruvenkatarajan et al. 2019¹³</p>	<ul style="list-style-type: none"> • Results: 42 euglycemic diabetic ketoacidosis (EDKA) and five cases of hyperglycaemic diabetic ketoacidosis (HDKA) were identified from 33 publications. <ul style="list-style-type: none"> ○ Canagliflozin was implicated in 26 cases. ○ Presentation time varied from a few hours up to six weeks after operation. ○ Precipitating factors may include diabetes medication changes, diet modifications and intercurrent illnesses. ○ There were 13 cases (12 EDKA and 1 HDKA) of bariatric surgery, 10 of them noted very-low-calorie diet regimens as a precipitating factor. ○ Seven patients required mechanical ventilation, and acute kidney injury was noted in five. ○ Outcome data were available in 32 cases, all of whom recovered completely. ○ No specific association between SGLT2-i cessation and the occurrence of DKA was identified. • Recommendations: <ul style="list-style-type: none"> ○ For healthy patients undergoing a short-stay procedure, SGLT2-i are withheld on the day of surgery and recommenced at 24 to 48 hours after the procedure along with adequate oral intake. ○ Minor surgical procedures, such as day surgery, may not require any temporary cessation of SGLT2-i or cessation only on the day of the procedure. ○ A much longer duration of withholding SGLT2-i may be needed in perioperative patients where oral intake is likely to be delayed, such as cardiac or abdominal surgery where postoperative ileus is common. ○ When SGLT2-i is administered in combination with other oral-glucose-lowering agents, strategies should be in place to manage the impact of them being withheld in conjunction with SGLT2-i. ○ SGLT2-i should not be commenced until the postoperative catabolic state is overcome by adequate oral intake. • Conclusion: Understanding this clinical entity and vigilance towards monitoring plasma/capillary ketones help in early identification and management.
<p>Predisposing factors for the development of diabetic ketoacidosis with lower than anticipated glucose levels in type 2 diabetes patients on SGLT2-inhibitors: a review</p> <p>Bamgboye et al 2020⁹</p>	<ul style="list-style-type: none"> • Study design: review • Methods: studies involving SGLT2-i medications in patients with type 2 diabetes and those that focused on DKA published up to 2020 were included. • Results: <ul style="list-style-type: none"> ○ Surgery is one of the major conditions associated with euglycaemic DKA with SGLT2-i ○ There are variations in the recommendations for the time period for withdrawal of SGLT2-i before surgery, ranging from 24 hours prior to 72 hours. ○ Local guidelines for safe perioperative procedures in patients on SGLT-2-i therapy should be developed and these guidelines should be communicated appropriately.

	<ul style="list-style-type: none"> • Conclusion: predisposing factors for developing euglycaemic diabetic ketoacidosis include withholding the use of SGLT2-i for less than 48 hours perioperatively.
<p>SGLT2 inhibitors: a systematic review of diabetic ketoacidosis and related risk factors in the primary literature</p> <p>Burke et al. 2017¹⁰</p>	<ul style="list-style-type: none"> • Study design: systematic review • Methods: case reports of SGLT2-i–related DKA were searched. • Results: 34 case reports of patients with type 1 and type 2 diabetes mellitus who developed DKA while receiving SGLT2-i were included. <ul style="list-style-type: none"> ○ The average blood glucose level on presentation for SGLT2-i–induced DKA was 265.6 ± 140.7mg/dl (14.7 ± 7.8mmol/L), with common symptoms including nausea, vomiting and abdominal pain. • Conclusion: common precipitating factors included patients who were diagnosed with type 2 diabetes and were subsequently found to have latent autoimmune diabetes of adulthood, patients who had recently undergone major surgery, or patients who had decreased or discontinued insulin.
<p>Evolving evidence of diabetic ketoacidosis in patients taking sodium-glucose cotransporter 2 inhibitors</p> <p>Fleming et al. 2020¹⁴</p>	<ul style="list-style-type: none"> • Study design: review • Methods: Ovid MEDLINE and Embase were searched in July 2019 for studies on SGLT2-i and DKA. • Results: Precipitating factors identified in SGLT2-i–associated DKA: <ul style="list-style-type: none"> ○ surgical stress ○ limited perioperative withholding of SGLT2-i ○ insufficient pre and postoperative or reduced dose of insulin ○ reduced perioperative oral intake ○ preoperative low-carbohydrate diets, such as for bariatric surgery ○ concurrent illness ○ infection ○ malignancy ○ dehydration and decreased oral intake ○ alcohol use ○ recent initiation of SGLT2-i therapy. • Suggestions for SGLT2-i withholding and SGLT2-i–associated DKA identification and management escalation in perioperative and unwell patients, based on the scant evidence available for: <p>Elective surgery patients:</p> <ul style="list-style-type: none"> ○ Withhold at least 3 days before surgery (day of and 2 days prior). ○ When a combination tablet is used, continue the other component (DPP4i or metformin) until the day prior to surgery or as per local guidelines. ○ In patients who have elevated HbA1c >9%, consider review of glycaemic stability before non-urgent surgery. ○ If patients are unwell on the day of surgery, postponement should be considered due to increased risk of DKA in concurrent illness ○ Monitor patients closely pre and postoperatively for signs of developing DKA.

	<p>Additional points in non-elective surgical patients:</p> <ul style="list-style-type: none">○ Withhold SGLT2-i as soon as a decision is made to proceed with surgery.○ Discuss with endocrinology/anaesthetics/critical care before surgery to communicate recent use of SGLT2-i and increased risk of DKA.○ Closely monitor fasting status of patients waiting for emergency surgery and avoid prolonged fasting, if possible. <p>Recommencing SGLT2-i:</p> <ul style="list-style-type: none">○ When eating and drinking well, ideally on discharge.○ Provide written advice to patients about seeking medical help if unwell in the week following procedures, signs and symptoms of DKA, as well as the benefits of ongoing therapy.○ If DKA has occurred, discuss ongoing medication use with endocrinology/medication prescriber prior to discharge.
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Source	Summary		
Grey literature			
	Peri procedure	On admission	Post procedure
Alert update September 2020 Peri-procedural Diabetic Ketoacidosis (DKA) with SGLT2 inhibitor use Australian Diabetes Society (ADS) and New Zealand Society for the Study of Diabetes (NZSSD). September 2020 ¹⁶	Cease SGLT2-i at least 3 days (2 days before procedure and the day of procedure) pre-procedure if the patient requires: <ul style="list-style-type: none"> one or more days in hospital “bowel preparation”. Cease SGLT2-i on the day of procedure if the patient: <ul style="list-style-type: none"> requires day procedure. Fasting before and after procedure should be minimised.	Consider ceasing procedures if: <ul style="list-style-type: none"> patient unwell non-urgent. If SGLT2-i has not been ceased 3 days prior or on the day, the course of action depends on: <ul style="list-style-type: none"> the urgency of the procedure patient comorbidity, surgical factors, HbA1c, blood ketones, and base-access. All patients on SGLT2-i undergoing emergency surgery should be admitted post-procedure to a ward.	Restart SGLT2-i only when: <ul style="list-style-type: none"> patient is eating and drinking normally close to discharge from hospital. Patients who have surgery/procedures should only restart if: <ul style="list-style-type: none"> on full oral intake consider delaying recommencement of SGLT2-i for a further 24 hours but also consider potential for hyperglycaemia provide written advice.
Sodium glucose co-transporter 2 inhibitors Therapeutic Goods Admission (TGA). July 2018 ¹⁵	Treatment with an SGLT2-I should be ceased before a major surgery.		Treatment may be restarted once the patient's condition has stabilised following surgery and oral intake is normal.
Guideline for perioperative care	Omit on day before surgery.		

Source	Summary		
Grey literature			
<p>for people with diabetes mellitus undergoing elective and emergency surgery</p> <p>Centre for Preoperative Care, Academy of Medical Royal Colleges. March 2021¹⁸</p>	<p>People with diabetes who are required to follow a reduced-calorie diet before their surgical procedure, such as in bariatric surgery or those who require bowel preparation preoperatively. For these cases, a longer period of treatment cessation may be necessary and, in general, should coincide with the reduced food intake.</p>		
<p>Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021)</p> <p>Dashora, et al. January 2021¹⁹</p>	<p>Suspend SGLT2-i in the following circumstances:</p> <ul style="list-style-type: none"> • admission for elective surgery • procedure requiring starvation. 	<p>Alternative diabetes treatment may be required in the interim.</p>	<p>Restart SGLT2-i only AFTER the patient has been eating normally for AT LEAST 24 hours AND no longer acutely unwell.</p>

Source	Summary		
Grey literature			
Manage diabetes and comorbidities with a joined-up strategy Dr Umesh Dashora and colleagues from the CaReMe UK Partnership. May 2021 ²⁰	Stop taking an SGLT2-i 24 hours before elective surgery requiring starvation and restart 24–48 hours after normal oral intake—which may take 1–2 weeks	Alternative glucose-lowering therapy may be needed during this period of interruption.	Restart SGLT2-i only after the patient is back to normal and eating and drinking.
Peri-operative management of the surgical patient with diabetes 2015 The Association of Anaesthetists of Great Britain & Ireland. September 2015, updated in 2019 ²¹	Day prior admission: <ul style="list-style-type: none"> • Take as normal 	Do not take on the day of surgery	Stop until eating and drinking normally
Management of adults with diabetes undergoing surgery and elective procedures: Improving standards summary Joint British Diabetes Societies for inpatient care (JBDS-IP). March 2016 ²²	Day prior admission: <ul style="list-style-type: none"> • Take as normal 	Omit on day of surgery	Omit until eating and drinking normally

Source	Summary		
Grey literature			
<p>FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections</p> <p>The Food and Drug Administration (FDA). December 2015, updated April 2020¹⁷</p>	<p>Canagliflozin, dapagliflozin and empagliflozin each should be stopped at least three days before, and ertugliflozin should be stopped at least four days before scheduled surgery.</p>		

Appendix

PubMed search terms

Q1. (SGLT2 OR "sodium-glucose cotransporter 2") AND ("Diabetic ketoacidosis"[MeSH Terms] OR "diabetic ketoacidosis"[Title/Abstract] OR "DKA"[Title/Abstract]) AND (surgery[MeSH Subheading] OR surg*[Title/Abstract] OR peri*[Title/Abstract] OR inpatient[Title/Abstract] OR admission[Title/Abstract])

98 studies retrieved on 26 August 2021

Q2. ((guideline[Publication Type]) OR (guideline*[Title] OR guidance*[Title] OR recommendation*[Title])) AND ((SGLT2 OR "sodium-glucose cotransporter 2"))

59 studies retrieved on 26 August 2021

Inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> • Published in English • Published since 2000 • Population: Diabetes in an inpatient setting • Intervention: SGLT2-inhibitors • Comparison: n/a • Outcomes: safety, DKA, clinical outcomes such as morbidity/mortality and other relevant outcomes • Study types: • Reporting empirical data <ul style="list-style-type: none"> ○ Reviews with systematic search strategy/methods ○ Randomised or non-randomised clinical trials ○ Guidelines and consensus statements 	<ul style="list-style-type: none"> • Not in English • Published prior to 2000 • Studies that do not meet PICOS criteria • Study protocols, conference abstracts • Case reports (case report studies published before 2019 were summarised within two systematic reviews included in this evidence check)

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