Evolving Evidence of Diabetic Ketoacidosis in Patients Taking Sodium-Glucose Cotransporter 2 Inhibitors

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Introduction: Sodium glucose cotransporter 2 inhibitors (SGLT2i) have emerged as an important class of blood glucose–lowering medications, due to cardiovascular, metabolic, and renal benefits. However, there is a small but significant risk of diabetic ketoacidosis (DKA) associated with their use.

Methods: A literature search was conducted in Ovid MEDLINE and Embase to July 2019 using variants on the key search terms *sodium-glucose cotransporter 2*, *diabetic ketoacidosis*, and *type 2 diabetes*. A broad spectrum of evidence was incorporated to facilitate a comprehensive narrative review. Further sources were identified through hand searching of reference lists.

Discussion: Although cardiovascular outcome trials demonstrated mixed evidence of SGLT2i associated DKA, increasing evidence from case reports and cohort studies has identified an increased risk. SGLT2i use is associated with a ketotic state caused by an increased glucagon:insulin ratio and stimulated by factors including stress-induced hormonal changes, insufficient insulin, decreased glucose, increased ketone resorption, and hypovolemia. Atypical presentations of DKA with lower-than-expected blood glucose levels are possible with SGLT2i use, so clinical and biochemical monitoring is vital for early identification and management. DKA risk is particularly increased with precipitating factors, therefore optimization of risk factors is vital. Recommendations for perioperative and sick day management of patients taking SGLT2i have been suggested based on available evidence.

Conclusion: SGLT2i are an excellent class of drug in the physician's toolkit for managing type 2 diabetes. However, both clinicians and patients must be aware of the potential for DKA and the need for increased monitoring, both clinically and biochemically, when potential precipitating factors are present. In acutely unwell patients, these medications should be withheld to reduce the risk of DKA. **(*J Clin Endocrinol Metab* 105: 2475–2486, 2020)**

Key Words: Sodium glucose cotransporter 2 inhibitors, diabetic ketoacidosis, perioperative, type 2 diabetes

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Abbreviations: AKI, acute kidney injury;BGL, blood glucose level;DKA, diabetic ketoacidosis;eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; SGLT2, sodium glucose cotransporter 2;SGLT2i, sodium glucose cotransporter 2 inhibitor;UACR, urinary albumin:creatinine ratio.

Diabetes is a major contributor to morbidity and mortality worldwide. In Australia, it is a leading cause of total burden of disease and the sixth leading underlying cause of death (1). Optimization of diabetes management is necessary for improved health outcomes, as is awareness and management of diabetes complications. Since 2013, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a very important class of blood glucose–lowering medication, as they have cardiovascular and renoprotective properties and they reduce mortality (2). Since their introduction, there has been an association between SGLT2i and increased risk of diabetic ketoacidosis (DKA), particularly in unwell or perioperative patients (3, 4). Diabetic ketoacidosis is traditionally characterized as hyperglycemia, metabolic acidosis, and ketonemia; however, cases associated with SGLT2i can be atypical, with lower-than-expected blood glucose, leading to delayed identification and management. This association is relevant for hospital medical staff who are responsible for pre-admission of surgical patients and perioperative care, emergency medicine practitioners, endocrinologists, and general practitioners (GPs) who are primarily responsible for medication prescription and patient education.

SGLT2s are primarily located in the first section of the proximal tubule of the kidney and are responsible for ~90% of sodium reabsorption (5). Inhibition of SGLT2 blocks secondary active transport of glucose from the lumen into cells along a sodium gradient created by the sodium-potassium adenosine triphosphate (Na+/K+ ATPase) transporter (6). Glycosuria is rapidly induced, leading to a reduction in glycated hemoglobin A1c (HbA1c) of approximately 0.6% to 0.9% (5). In Australia, SGLT2i empagliflozin (Jardiance), dapagliflozin (Forxiga), and ertugliflozin (Steglatro) have both Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Scheme (PBS) approval for use in type 2 diabetes. Local and international guidelines recommend SGLT2i as a second-line agent after metformin for patients with atherosclerotic cardiovascular disease, heart failure, or kidney disease, with combination tablets of metformin-empagliflozin (Jardiamet), metformin-dapagliflozin (Xigduo), and metformin-ertugliflozin (Segluromet) facilitating this treatment (7, 8). SGLT2i are also available in combination with dipeptidyl peptidase-4 inhibitors (DDP4i) for dapagliflozin-saxagliptin (Qtern), empagliflozin-linagliptin (Glyxambi), and ertugliflozin-sitagliptin (Steglujan). (4). The increasing use of SGLT2i is due to evidence from large, multicenter trials demonstrating reduced cardiovascular and renal morbidity and mortality in people with type 2 diabetes taking these medications (8-10). Evidence is also emerging for reduced morbidity and mortality associated with heart failure in people without diabetes (11).

The purpose of this review is to provide a narrative background and up-to-date evidence for the risk of DKA in people with type 2 diabetes taking SGLT2i, as well as recommendations for identification and prevention of DKA in patients who are unwell or in the perioperative period based on available evidence. Given the morbidity and mortality associated with DKA and the potential for atypical clinical presentations, prevention, early identification, and appropriate management are vital. Patients taking SGLT2i have often been described as presenting with "euglycemic DKA." As this term may be confusing in clinical settings depending on local interpretation of euglycemia, we have elected to describe these presentations as having lower-than-expected blood glucose levels (BGL).

Methods

A search was conducted in OVID and MEDLINE from database inception to June 2019, using variants of keywords *sodium-glucose cotransporter 2*, *diabetic ketoacidosis*, and *type 2 diabetes*. Further hand searching of the literature was conducted to identify relevant alerts, guidelines, safety trials, case reports, case series, and systematic reviews. A broad spectrum of evidence was prioritized in order to facilitate a comprehensive narrative review.

Benefits of SGLT2i

The metabolic, cardiovascular, and renal benefits of SGLT2i have been extensively investigated in order to meet regulatory requirements for novel hypoglycemic agents (Table 1). The metabolic benefit of SGLT2i is due to a glycosuria-induced caloric deficit of 250 to 450 kcal/day, with weight loss of more than 2 kilograms over 6 to 12 months reported (5, 12). In key cardiovascular outcome trials, there was a reduced incidence of the combined endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke in empagliflozin and canagliflozin, with noninferiority for cardiovascular adverse events demonstrated in dapagliflozin, and a reduced risk of hospitalization for heart failure for all 3 medications (Table 1) (13-16). Relative reduction in heart failure and ischemic event outcomes was consistent across all trials; however, the reduction in risk of heart failure outcomes was greater than in ischemic events including myocardial infarction and stroke (9). Furthermore, in patients with and without diabetes, with heart failure and an ejection fraction of 40% or less, the use of dapagliflozin 10 mg daily in addition to patients' pre-existing

Table 1. Cardiovascular and Renal Benefits of SGLT2i in Cardiovascular Outcome Trials

Trial	Cardiovascular Benefits		Renal Benefits
	Risk of combined MACE outcome	Risk of hospitalisation for heart failure	
Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus (EMPA-REG OUTCOME) trial	Significantly reduced (HR, 0.86; 95% CI, 0.74-0.99; $P = 0.04$ for superiority)	Significantly reduced (HR, 0.65; 95% CI, 0.50-0.85; $P = 0.002$)	Significantly reduced renal composite outcome (HR, 0.54; 95% CI, 0.50-0.75; $P < 0.001$)
Canagliflozin Cardiovascular Assessment Study (CANVAS) Program	Noninferior (HR, 0.86; 95% CI, 0.75-0.97; $P = 0.08$)	Significantly reduced (HR, 0.67; 95% CI, 0.52-0.87; $P = 0.02$)	Significantly reduced renal composite outcome (HR 0.60; 95% CI, 0.47-0.77; P value not calculated)
Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)	Significantly reduced (HR, 0.80; 95% CI, 0.67-0.95; $P = 0.01$)	Significantly reduced (HR, 0.61; 95% CI, 0.47-0.80; $P < 0.001$)	Significantly reduced renal composite outcome (HR, 0.70; 95% CI, 0.59-0.82; $P = 0.00001$)
Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial	Noninferior (HR, 0.93; 95% CI, 0.84-1.03; $P = 0.17$)	Significantly reduced (HR, 0.073; 95% CI, 0.61-0.88; $P = 0.0008$)	Significantly reduced renal composite outcome (HR, 0.53; 95% CI, 0.43-0.66; $P < 0.001$)

Renal composite outcomes defined for each trial as: EMPA-REG OUTCOME (doubling of serum creatinine (Cr) with estimated glomerular filtration rate (eGFR) ≤45, renal-replacement therapy, or renal death), CANVAS (sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes), CREDENCE renal composite outcome (primary composite outcome of end-stage kidney disease, doubling of the serum Cr level, or renal or cardiovascular death), DECLARE-TIMI 58 renal composite outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2 of body surface area, new end-stage renal disease, or death from renal or cardiovascular causes).
Abbreviations: ACR, albumin:creatinine ratio; CI, confidence interval; ESKD, end-stage kidney disease; ESRF, end-stage renal failure; HR, hazard ratio; MACE, major adverse cardiovascular events.

management has recently demonstrated a significant reduction in a composite outcome of worsening heart failure or death from cardiovascular causes (HR, 0.74; 95% CI, 0.65-0.85; $P < 0.001$) (11). While the mechanism behind these findings is not yet clear, it may be partially explained by volume contraction secondary to diuresis leading to a reduction in blood pressure of 4-6mmHg, lowering of blood glucose and weight loss (5). Significant renal benefits of canagliflozin included reduced risk of death from renal causes (14, 16) and reduced risk of progression to end-stage kidney disease. Serum creatinine and mean urinary albumin:creatinine ratio (UACR) were also decreased (Table 1) (16). Empagliflozin was shown to delay initiation of renal replacement therapy and progression of nephropathy with decreased macroalbuminuria and serum creatinine (13). Dapagliflozin also showed a slower deterioration of UACR (17). It has been suggested that UACR is a risk predictor for renal events and for cardiovascular outcomes (9). As the metabolic, cardiovascular, and renal complications of diabetes may significantly increase the burden for people with diabetes, slowing progression of the condition and its complications is key for optimizing management.

Adverse Effects of SGLT2i

Potential adverse effects of SGLT2i use must also be considered to ensure appropriate use. There have been reports of genito-urinary infections, acute kidney injury (AKI), and limb amputation with SGLT2i use, in addition to an increased risk of DKA. Genital mycotic infection and urinary tract infections were observed in both men and women in canagliflozin in a phase 3 trial (18). Further trials have not demonstrated an increased risk of urinary tract infection (14); however, there is evidence for a significantly increased risk of mycotic genital infections with dapagliflozin and empagliflozin (19, 20) and rare post-marketing reports of Fournier's gangrene in both men and women (21). While there have also been post-marketing reports of AKI in cardiovascular outcome trials for both empagliflozin and dapagliflozin, clinical trials reported no significant increase in AKI (19, 20). Regarding amputations, the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed almost double the risk of atraumatic lower extremity amputations compared with placebo, with 79% of amputations below the ankle (22). Both infective and acute ischemic etiologies were identified, although the

underlying mechanism for the increased risk is unclear (22). A similar risk has not been identified with empagliflozin or dapagliflozin. An increased risk of DKA has been identified through cardiovascular outcome trials, case reports, and increasingly through adverse event databases as discussed below. With increasing use of SGLT2i, further research is required to firmly establish the low risk of adverse effects and encourage appropriate identification and management in all medical settings.

Potential Mechanisms Underlying Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i

Traditional DKA consists of hyperglycemia (BGL > 13.9 mmol/L), metabolic acidosis (pH < 7.3 or bicarbonate < 18 mmol/L), and ketonemia due to insulin deficiency, either relative or absolute, and increased counter-regulatory hormones in people with type 1 and type 2 diabetes (3, 23). It may be important to incorporate base excess < −5 mmol/L into the diagnostic criteria to assess the metabolic component of acidosis. Insulin deficiency leads to increased gluconeogenesis and glycogenolysis, decreased peripheral glucose utilization, and increased lipolysis, increasing production and retention of both glucose and ketone bodies (Fig. 1) (3, 23). However, in patients taking SGLT2i, DKA may be precipitated by reduced insulin requirements, due to increased urinary glucose excretion and SGLT2i-stimulated release of glucagon from pancreatic alpha cells (24, 25). This shifts the insulin:glucagon ratio in favor of glucagon, leading to increased lipolysis due to the loss of the antilipolytic effect of insulin, as well as the stimulation of lipase by glucagon creating an augmented free fatty acid substrate for hepatic synthesis of ketone bodies (26, 27). Glucagon also stimulates the hepatic beta-oxidation of free fatty acids into acetyl CoA required for ketone body metabolism, further increasing ketone concentrations (26, 27). Plasma ketone levels are maintained, as ketone body reabsorption is normally high and may be further compounded by the impact of SGLT2i on the sodium gradient in the proximal lumen (27). This may be exacerbated by the mild osmotic diuretic effect caused by SGLT2i. It is important to note that DKA can also occur in individuals with type 2 diabetes who are not taking SGLT2i; therefore, the diagnosis is not excluded in unwell or deteriorating patients with type 2 diabetes who are not taking these medications.

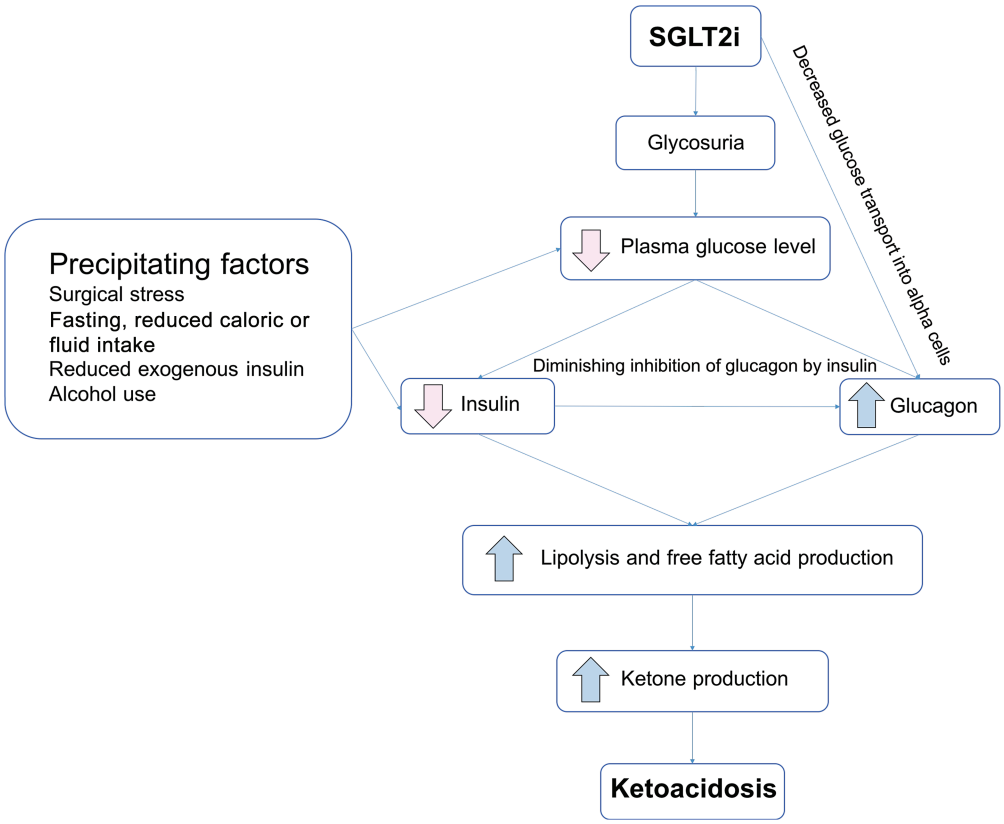

Figure 1. Potential mechanism of SGLT2i-associated diabetic ketoacidosis and contribution of precipitating factors. Reproduced with permission from Libianto R, Davis TM, Ekinci EI. Advances in type 2 diabetes therapy: a focus on cardiovascular and renal outcomes. *Med J Aust.* 2020;212(3):133-139.

Table 2. Precipitating Factors Identified in SGLT2i-Associated DKA

Precipitating Factors Identified in SGLT2i-Associated DKA
Surgical stress (35-40)
Limited perioperative withholding of SGLT2i (35, 39-41)
Insufficient pre- and postoperative (42) or reduced dose of insulin (43, 44)
Reduced perioperative oral intake (45)
Preoperative low carbohydrate diets, such as for bariatric surgery (41, 42)
Concurrent illness
Infection (46-50)
Malignancy (43, 51)
Dehydration and decreased oral intake (43, 52-54)
Alcohol use (49, 55)
Recent initiation of SGLT2i therapy (56)

Diabetic ketoacidosis (DKA) has been precipitated following major procedures such as coronary artery bypass grafts (35), general surgeries including bariatric surgery (36-38), and other major surgeries (39, 40). Further perioperative factors include limited withholding of SGLT2i (35, 39-41), insufficient pre- and postoperative insulin (42), reduced oral intake including nil-by-mouth regimens (45) and low carbohydrate diets for bariatric surgery (41, 42). Other precipitants include concurrent illness, including infection (46-50) and malignancy (43, 51), reduced insulin (43, 44), decreased oral intake (52-54), dehydration (43), and alcohol use (49, 55). DKA has also occurred with recent initiation of SGLT2i (56).

Precipitating Factors of Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i in the Setting of Surgery and Illness

Precipitating factors have been identified that may further increase the risk of DKA in patients taking SGLT2i (Table 2). Surgery and illness induce a stress response that is associated with increased insulin requirements and lipolysis (Fig. 1) (3, 28). The stress response increases secretion of growth hormone, inhibiting glucose uptake and use, and cortisol, promoting gluconeogenesis (3, 29). This creates a hyperglycemic state (29). Meanwhile, increased secretion of growth hormone, glucagon, and cortisol leads to enhanced lipolysis, increasing the free fatty acid substrate for ketone body production (3, 29). In patients treated with dual SGLT2i and insulin therapy, increased renal glucose excretion causing lower blood glucose levels may lead to reduced insulin dosing in order to avoid hypoglycemic events (30). However, decreased insulin dosing may be insufficient to suppress lipolysis and ketogenesis, thereby increasing the risk of DKA (3, 30). In starvation states, lactate concentration is increased, inducing hepatic ketogenesis, while decreased carbohydrate intake, either through perioperative fasting or through provision of low carbohydrate diets for weight control, can lead to enhanced glucagon secretion from alpha cells in the pancreas and decreased insulin secretion (31, 32). Furthermore, decreased fluid intake may impair renal function, leading to decreased excretion of glucose and ketones, thereby increasing glycemia and the ketotic state and exacerbating a positive feedback loop of worsening metabolic acidosis (23). These factors are commonly present in the perioperative period but also need to be considered in unwell patients during emergency and medical presentations (33, 34). As patients may present with multiple concurrent factors and various clinical presentations, awareness of these mechanisms is vital for identifying, preventing, and managing DKA in patient taking SGLT2i. Further research is required to assess the inpatient safety profile of SGLT2i; however, this is complicated as these medications may be ceased during admissions due to the overlap between features of illness and precipitating factors of SGLT2i-associated DKA (34).

Cardiovascular Outcome Trial Evidence for Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i

In initial SGLT2i cardiovascular outcome trials, evidence for DKA in people with type 2 diabetes taking these medications was mixed (Table 3). Empagliflozin demonstrated a nonsignificant increase in DKA, dapagliflozin a significant increase, and canagliflozin has demonstrated mixed findings (14, 15, 19, 20). Eighty percent of people who developed DKA while taking dapagliflozin were also taking baseline insulin (19). Evidence was also mixed in pooled analyses from clinical trials. In empagliflozin phase 1 to phase 3 clinical trials, DKA was present in 0.1% of people using placebo and 10 mg of empagliflozin, and in < 0.1% of patients taking 25 mg (57). However, elevated urinary ketones were identified in the empagliflozin group, suggesting an underlying ketotic state (57). In canagliflozin trials, DKA occurred in 0.02% of people with type 2 diabetes taking 100 mg of canagliflozin and 0.06% of patients taking 300 mg of canagliflozin versus 0.03% in the comparator group (58). Those with reported DKA had a longer duration of diabetes, lower BMI, higher HbA1c, and lower baseline estimated glomerular filtration rate (eGFR) (58). However, further pooled analysis

Table 3. Incidence of DKA in People With Type 2 Diabetes Taking SGLT2i in Cardiovascular outcome Trials

Trial	Participants	Incidence of DKA
Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus (EMPA-REG OUTCOME) trial	7020 (4687 randomized to empagliflozin, 2333 randomized to placebo)	0.1% (empagliflozin 10 mg) <0.1% (empagliflozin 25 mg) <0.1% (placebo)
Canagliflozin Cardiovascular Assessment Study (CANVAS) Program	9734 (5795 randomized to canagliflozin, 3447 randomized to placebo)	0.6 vs 0.3 participants with an event per 1000 patient-years; HR, 2.33; 95% CI, 0.76-7.17; *P* = 0.14
Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)	4401(2202 randomized to canagliflozin, 2199 randomized to placebo)	2.2 vs 0.2 participants with an event per 1000 patients-years; HR 10.80, 95% CI 1.39-83.65, *P* value not calculated
Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial	17 160 (8582 randomized to dapagliflozin, 8578 randomized to placebo)	0.3% vs 0.1%; HR 2.18; 95% CI, 1.10-4.30; *P* = 0.02

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; HR, hazard ratio.

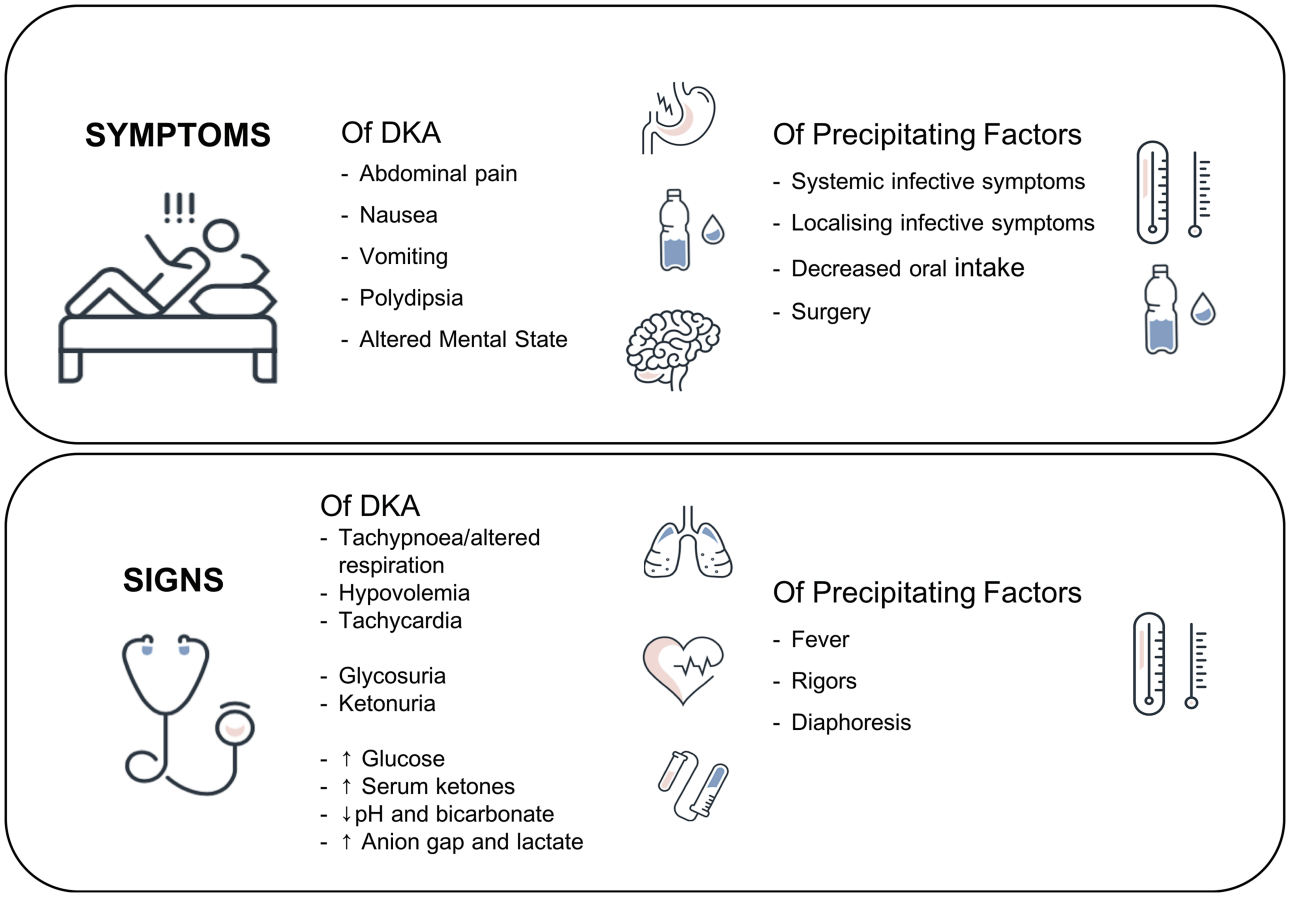

Figure 2. Signs and symptoms of DKA and potential precipitating factors in patients with type 2 diabetes taking SGLT2i.

of 21 dapagliflozin phase 2b/3 clinical trials identified only 1 episode of DKA in the dapagliflozin group with none in placebo, for a total estimated incidence of 0.02% (95% CI, 0.004-0.059) (59) Patient populations in these trials were highly screened, including for previous episodes of DKA, and therefore may not be representative of the all patients taking SGLT2i, possibly underestimating the true incidence.

Case Reports of Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i

Outside of cardiovascular outcome trials, increasing reports of DKA in people with type 2 diabetes taking SGLT2i, identified both in the literature and adverse event reporting systems, led to alerts in

several countries regarding potential risk. The first of these, released in 2015 by the US Food and Drug Administration (FDA), highlighted the need for patient and practitioner awareness, DKA symptoms, potential for lower-than-expected BGL presentations, and the need for caution when potential precipitating factors were present (60). This was followed by alerts from the Australian Diabetes Society regarding perioperative risk, the European Association for the Study of Diabetes and European Medicines Agency regarding the potential for atypical presentations and the need for further review, and guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology for identification and management of SGLT2i-associated DKA (61-63). The publicly available FDA adverse reporting system (FAERS) has provided valuable information regarding SGLT2i-associated DKA. Of all 14 966 cases of medication-associated DKA reported up to June 30, 2019, canagliflozin accounted for 3320 cases (22.26%), empagliflozin 1824 (12.19%), and dapagliflozin 1483 (9.9%) (64). Lower-than-expected BGLs were present in 374 cases of medication-associated DKA, with SGLT2i accounting for the majority of these (2.50%) (64). Analysis of data from the FAERS database estimated a 7-fold increased risk of DKA in people with type 2 diabetes taking empagliflozin, dapagliflozin, and canagliflozin compared with DPP4i (65). In case reports, patients often presented with undifferentiated symptoms including nausea, vomiting, abdominal pain, polyuria, anorexia, and myalgias (3, 42, 65, 66), while more unusual presentations such as generalized weakness (67) and altered mental state have been observed (68). The combination of atypical presentation and lower-than-expected BGLs may delay diagnosis until identification of anion gap metabolic acidosis and elevated serum ketones (3). Case reports have identified precipitating factors that may increase a patient's risk of developing DKA in the perioperative period (35-42, 45), in concurrent illness during hospital admissions and in the community (43, 44, 46-55), and with recent initiation of SGLT2i (56) (Table 2). Where no clear precipitant exists, testing for autoantibodies has revealed undiagnosed type 1 diabetes (42, 58, 69) or latent autoimmune diabetes in adults (LADA) who have an increased baseline risk (58, 70). However, other cases have occurred with no clear precipitant and no defining patient characteristics (71-73); a recent systematic review of perioperative DKA in patients taking SGLT2i identified a precipitant in only 57% of cases (42). This suggests that other unidentified factors may also drive susceptibility to DKA.

Further analysis of the risk of DKA and potential precipitating factors has been aided by national databases/registries. In a population of US patients, those taking SGLT2i had a significantly increased risk of DKA within 180 days of medication initialization (HR, 2.2; 95% CI, 1.4-3.6) compared with patients on DPP4i, after propensity score matching (74). In contrast to these studies, a prospective multicenter study of the Canadian Canagliflozin Registry of 527 SGLT2i-naïve people with type 2 diabetes identified no DKA events after 12 months (75). In Denmark, a nonsignificant risk of DKA was identified in people with type 2 diabetes on combination therapy (HR, 1.6; 95% CI, 0.7-3.5), with no events in patients on SGLT2i monotherapy (76). More recently, an Australian multicenter retrospective cohort study demonstrated a significant risk of DKA in patients taking SGLT2i compared with those on alternate therapies, with an incidence of 1.02 per 1000 (95% CI, 0.74-1.41 per 1000) in SGLT2i users and 0.69 per 1000 (95% CI, 0.58-0.82 per 1000) in non-SGLT2i users (OR, 1.48; 95% CI, 1.02-2.15; $P = 0.037$) (17). More patients on SGLT2i developed DKA during their inpatient stay (OR, 37.4; 95% CI, 8.0-175.9; $P < 0.0001$), with identified precipitants including fasting, dehydration, surgery, and infection (17). The evolving evidence continues to identify DKA as a rare but important risk SGLT2i that may be more likely to be precipitated by external factors outside of controlled trial populations.

Identifying Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i

DKA can be difficult to identify in people with type 2 diabetes using SGLT2i, since patients often present with undifferentiated symptoms such as abdominal pain, nausea, vomiting, and fatigue (61), which may be similar to symptoms of concurrent or chronic conditions, postoperative symptoms, or postoperative medication side effects. Furthermore, SGLT2i increase glucose clearance, contributing to presentations with lower-than-expected BGLs (< 13.9 mmol/L) (5), which may delay initiation of ketone testing. Therefore, rather than traditional hyperglycemia, acidosis, and ketosis, clinicians must monitor changes in patient signs and symptoms to prompt further assessment (Fig. 2). This is particularly complicated where the symptoms and signs of DKA may be similar to an exacerbation of underlying conditions (67), deterioration of a presumed diagnosis like sepsis (77), or when DKA itself may result from deterioration of the primary

presentation. Lower BGLs may present with less polyuria and polydipsia than traditional DKA, further clouding clinical identification (78). However, polyuria may also be an effect of SGLT2i use itself because of the promotion of glycosuria and the resultant osmotic effect of that. It is vital that clinicians consider DKA as a diagnosis in all unwell patients with type 2 diabetes taking SGLT2i, while also considering and investigating critical differentials. A high index of suspicion, increased monitoring including regular assessment of BGLs and serum or capillary ketones, early initiation of further investigation with venous blood gases (VBG) and consideration of base excess as a marker of the metabolic component of acidosis, as well as escalation of care through critical care/patient deterioration pathways, is vital when DKA is a differential diagnosis (Table 4). It is important to note that urinary ketones may be negative, because when testing ketones, high renal ketone reabsorption delays ketonuria (27), and urine ketone testing identifies the less prevalent ketone body acetoacetate, with readings potentially influenced by urine production and time of voiding (79). Therefore, capillary ketone testing at the bedside followed by formal serum ketone testing for beta-hydroxybutyrate is more accurate and recommended (4, 63).

Reducing the Risk of Diabetic Ketoacidosis in People With Type 2 Diabetes Taking SGLT2i

With an increasing awareness of the heightened risk of DKA in patients using SGLT2i, recommendations have been made to mitigate potential precipitating

Table 4. Suggestions for SGLT2i Withholding and SGLT2i-Associated Diabetic Ketoacidosis (DKA) Identification and Management Escalation in Perioperative and Unwell Patients, Based on the Scant Evidence Available

Elective surgery patients:
Withhold at least 3 days before surgery (day of and 2 days prior)
◦ There is limited evidence to support a reduced withholding time for minor surgeries with minimal fasting time
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 glycemic stability prior to nonurgent surgery
If patients are unwell on the day of surgery, postponement should be considered due to increased risk of DKA in concurrent illness
Check finger prick blood ketones in all patients on the day of surgery and increase frequency of blood ketone testing in the perioperative period
Patients with ketones > 1 mmol/L should have VBG prior to surgery and be discussed with the treating team, anesthetics and local endocrinologists/physicians prior to proceeding
If base excess is < –5mmol/L with ketones > 1.0 mmol/L, it is presumed the patient has DKA
If DKA is identified, escalate care urgently through discussion with endocrinology/physicians and critical care teams as appropriate within local protocols. Advice from tertiary centers should be sought if required.
Monitor patients closely pre-and postoperatively for signs of developing DKA
Ensure adequate hydration is maintained in fasting patients
In patients with elevated blood ketones, consider and optimize other factors potentially contributing to ketosis such as alcohol use or starvation
Additional points in nonelective surgical patients:
Withhold SGLT2i as soon as a decision is made to proceed with surgery
Discuss with endocrinology/anesthetics/critical care prior to surgery to communicate recent use of SGLT2i and increased risk of DKA
Closely monitor fasting status of patients waiting for emergency surgery and avoid prolonged fasting if possible
Unwell or deteriorating patients in the community, emergency department, or inpatient setting:
Withhold SGLT2i while patient is acutely unwell
Ensure urgent testing of finger prick blood ketones if DKA is suspected
If ketones > 1.0 mmol/L perform a VBG
If base excess < –5 mmol/L with ketones > 1.0 mmol/L, it is presumed the patient has DKA
If DKA is identified, escalate care as required to enable appropriate investigation and management of suspected DKA
Recommencing SGLT2i
When eating and drinking well, ideally on discharge
Provide written advice to patients with advice to seek medical advice 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

factors (Table 4). The first line in prevention is careful patient selection and continuing patient education. Antibody testing to exclude type 1 diabetes has been suggested, due to SGLT2i use revealing previously misdiagnosed patients (3, 42, 80). In the surgical setting, recommendations include comprehensive preoperative assessment, perioperative cessation of SGLT2i for the day of and 2 days prior to surgery, delaying of nonurgent surgery if SGLT2i have not been withheld and delayed postoperative restarting of SGLT2i until the patient has resumed normal eating (61). This timeframe has been suggested to account for the ~12.5-hour half-life of SGLT2i and the dose-dependent 24 to 48 hour offset time of SGLT2i (3, 5). However, there is ongoing discussion about the relationship between the magnitude of surgery and time to cessation, with suggestions that for minor procedures requiring minimal fasting, a smaller withholding period may suffice, although there is minimal evidence in this area (42). It has also been recommended that surgery should be postponed if SGLT2i have not been ceased, capillary ketones are > 1.0 mmol/L, or HbA1c > 9% (61). However, this can be logistically challenging, particularly for patients with limited access to medical care who have travelled long distances or those who have made complex domestic arrangements to enable the surgery to take place. Postoperatively, it has been recommended to restart SGLT2i only when patients have sufficient hydration and carbohydrate intake or immediately prior to discharge (61). In the community and during hospital admissions, it has been suggested that SGLT2i be withheld when sufficient hydration and carbohydrate intake is not possible, particularly at times of severe illness, and only restarted when regular oral intake has resumed (4). Additionally, patients should avoid very low carbohydrate or ketogenic diets and excessive alcohol intake to further reduce the risk of DKA (4, 8).

Moreover, in the perioperative period, the implementation of such recommendations is complicated by the urgency of nonelective operations for emergency presentations, delays to theater, and the potentially unclear presentation of DKA in many patients. The perioperative period naturally lends itself to many of the risk factors for DKA, including fasting, dehydration, and changes to medication schedules, including but not limited to appropriate insulin provision. Guidelines for perioperative monitoring of diabetes often account for scheduled, elective surgeries rather than emergency presentations with high variation in individual patient characteristics. Therefore, it is vital that factors that can contribute to the development of DKA are assessed and optimized prior to surgery and considered for postoperative planning, especially appropriate insulin, hydration, and oral intake (Table 2). In the community, appropriate withholding of medication and avoidance of ketogenic diets is reliant on thorough and ongoing patient education and awareness of the need for early presentation for medical care. In the case of critically unwell patients, early identification of SGLT2i use and potential contributors to DKA is vital for prompt cessation of SGLT2i therapy and commencement of DKA management protocols where indicated.

Management of Diabetic Ketoacidosis in Patients Taking SGLT2i

Once DKA has been identified in a patient, management should be initiated as soon as possible according to local protocols. Management of DKA involves provision of insulin and intravenous glucose, with insulin commonly being administered through intravenous infusion, to move the insulin:glucagon ratio away from a ketogenic state (81). Intravenous hydration may also be required to combat osmotic diuresis depending on clinical presentation/fluid status, and potassium replacement to account for the intracellular shift of potassium with initiation of insulin (81). As patients taking SGLT2i may have lower-than-expected BGL, they may require more intravenous glucose initially once insulin is initiated than those who present with hyperglycemia. This is crucial, as hypoglycemia leads to greater mortality in hospitalized patients with diabetes (82). Input from endocrinology or experienced physicians and intensivists should be sought for all patients with DKA, either through a hospital-based team or advice from a referral center, depending on location and local protocols, to allow for appropriate escalation of care. Following resolution of DKA, patients should be provided with written and verbal information about DKA and signs/symptoms to monitor in case of recurrence.

Engagement with clinicians is important both to increase awareness of clinical presentations that may have a greater risk of DKA for people with type 2 diabetes taking SGLT2i and to facilitate further research. In an Australian case series, physicians in 6 of 13 DKA patients were unaware of any connection between DKA and SGLT2i, while in 2 cases the diagnosis was initially overlooked (80). Furthermore, diagnosis of DKA has been delayed up to 4 days, with patients undergoing extensive investigation, including imaging, prior to a biochemical diagnosis (42) and it has been suggested that the actual incidence of DKA may be higher than

Table 5. Take home messages

SGLT2 inhibitors are excellent agents for improving glycemic management while providing cardiovascular, metabolic and renal benefits
There is a small but significant risk of DKA associated with their use
SGLT2i associated DKA may present with atypical signs/symptoms and lower than expected blood glucose levels
The potential for DKA is increased when precipitating factors including illness, infection, surgical stress, decreased insulin, and decreased oral intake are present
The risk of DKA can be decreased with:
Careful patient selection and thorough patient education about DKA risk
Temporary withholding of SGLT2i for three days before major surgery and colonoscopy
Withholding of SGLT2i in unwell patients requiring admission to hospital
Increased clinician and patient awareness of atypical presentations of DKA
Increased monitoring when precipitating factors are present
Early investigation when patients may be developing DKA
Early engagement with endocrinology/critical care teams for management and support
Recommencing SGLT2i postsurgery when patients are eating well again is important as these agents have cardiovascular (secondary prevention) and renal benefits and reduce morbidity and mortality
DKA can also occur in patients with type 2 diabetes who are not taking SGLT2i, therefore the diagnosis must still be considered in unwell or deteriorating patients

published and reported (83). Therefore, greater clinician awareness of precipitants that may influence the risk of DKA in people with type 2 diabetes taking SGLT2i, difficulties in identifying DKA in SGLT2i, and ways to minimize this risk are needed.

Conclusion

SGLT2i have well-defined cardiovascular, metabolic, and renal benefits for an increasing number of people with diabetes, as these medications are more widely prescribed and may have an even broader role in people with heart failure. With evidence emerging of improved heart failure outcomes in people without diabetes, this number will only continue to rise. Therefore, the small but significant risk of DKA in those taking SGLT2i in the presence of precipitating factors must be considered by clinicians and highlighted in ongoing patient education (Table 5). Further research is required to quantify the full extent and risk of precipitating factors and patient demographics that may contribute to DKA presentations. Clarification of the mechanism for this increased risk is also required to allow for thorough selection and monitoring of patients who will benefit from the addition of SGLT2i to their diabetes management. Ongoing assessment and review of recommendations for reduced risk of DKA in the perioperative, medical, and community settings is required to ensure optimal risk management.

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Additional Information

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