Summary: Patients taking SGLT2 inhibitors may experience a rare but serious complication called euglycemic diabetic ketoacidosis (EDKA). Holding these medications for 3-4 days is required prior to elective procedures.

SGLT2i (sodium-glucose cotransporter-2 inhibitors) are a class of oral antidiabetic agents often used in conjunction with metformin or other antidiabetic medications for the treatment of type 2 diabetes mellitus (T2DM). SGLT2i are also used for reasons other than glucose control in patients with or without diabetes due to their beneficial effects on cardiovascular and renal diseases. SGLT2i decrease serum glucose levels by inhibiting glucose reabsorption from the kidney's proximal renal tubule. This leads to increased glycosuria and decreased plasma glucose levels. This class of medications has a low risk of hypoglycemia because SGLT2i only influence circulating glucose (not intracellular glucose).

The following are the generic and trade names of the currently available SGLT2 inhibitors:

- canagliflozin (Invokana)
- dapagliflozin (Farxiga)
- empagliflozin (Jardiance)
- bexagliflozin (Brenzavvy)
- ertugliflozin (Steglatro)

The SGLT2i class has been associated with EDKA under several conditions including, but not limited to, the stress of surgery and fasting (NPO or low PO intake states). In addition to these stressors, EDKA events are also associated with infections, trauma, myocardial infarctions, and excessive alcohol intake. What makes this an even more challenging issue is the potential for delayed diagnosis due to normal or slightly above normal serum glucose levels. The diagnosis of EDKA may be difficult because of the absence of extremely high serum glucose levels that typically accompany DKA. It is important to note that patients on SGLT2i may experience hyperglycemic DKA as well as euglycemic DKA.

Predisposing factors for EDKA:

- Surgical/procedure associated stress
- Dehydration (fasting)
- Reduced carbohydrate intake (fasting)
- Concurrent illness, including infections
- Alcohol intake

Signs and symptoms of EDKA:

- Ketoacidosis: pH <7.3, bicarbonate <18 mmol/L, anion gap >14 mEq/L
- Euglycemia: blood sugar <250 mg/dL (if glucose ≥250 mg/dL then could be DKA)
- Positive serum or urine ketones
- Nausea/vomiting
- Tachypnea (Kussmaul breathing)
- Tachycardia
- Abdominal pain

- Altered mental status

Evaluation for EDKA:

- Arterial blood gas for metabolic acidosis
- Basic metabolic panel
- Serum ketones (beta hydroxybutyrate)
- Exclusion of other causes of high anion gap metabolic acidosis

Treatment of EDKA/DKA

- Rehydration
- Insulin + dextrose infusion
- Electrolyte replacement
- Consultation with Endocrinology Service should be considered

Our recommendations for the care of patients on SGLT2i are as follows:

A. Discontinue SGLT2 inhibitors 3-4 days prior to all surgeries/procedures. Patients should be given clear instructions about this at pre-surgical testing or by their gastroenterologist/primary care physician prior to bowel preps.

- Canagliflozin (Invokana) – Hold 3 days
- Dapagliflozin (Farxiga) – Hold 3 days
- Empagliflozin (Jardiance) – Hold 3 days
- Bexagliflozin (Brenzavvy) – Hold 3 days
- Ertugliflozin (Steglatro) – Hold 4 days

B. Cases in which high interventional stress may be expected and/or where a prolonged fasting state is expected in the peri-procedure period (>12 hours) increase the risk for EDKA due to decreased glycogen stores.

a. Elective procedures should be cancelled/postponed if SGLT2i medication is taken inadvertently (within the 3-4 day recommended hold period) where a prolonged fasting state is expected in the peri-procedure period.

b. Exceptions may include patients undergoing short (<45 minutes) very low risk procedures where postprocedural oral intake can occur within this 12-hour fasting window (also see sections D and E below).

C. Patients who inadvertently take their SGLT2i prior to undergoing colonoscopy should be rescheduled as the bowel prep itself could put them at risk for EDKA. Exceptions may be made at facilities that have access to point of care ketone and chemistry or blood gas testing as described in section E below.

a. Such patients should be assessed for any signs/symptoms of DKA.

b. If there is any indication of DKA on clinical assessment, then the patient should be referred to the nearest emergency department or seen by an endocrinologist for further evaluation.

c. In the absence of clinical evidence of DKA, patients should resume oral carbohydrate and fluid intake as soon as possible and return home.

D. If the medication is taken inadvertently and a procedure is deemed by the clinical team to be urgent enough to proceed, the procedure should be performed at a facility that has the ability to obtain the below labs:

a. Basic metabolic panel (check anion gap and bicarbonate) or VBG/ABG (check pH), and beta hydroxybutyrate (serum ketones). Point of care (POC) testing is acceptable.

b. Close monitoring for EDKA is recommended and appropriate lab work should be obtained pre and post procedure. For cases that have an expected duration of >4 hours, lab testing should be performed intraoperatively on a Q4 hour basis.

E. For locations that have point of care ketone and chemistry or blood gas testing the following algorithm may be implemented:

a. If the patient shows any signs or symptoms of DKA at any point leading up to the procedure, then the procedure should be cancelled and the patient should be sent to the nearest emergency department or seen by an endocrinologist for further evaluation.

b. If the ketone level is <1.5 mmol/L, then the procedure can continue as scheduled.

c. If the ketone level is ≥1.5 mmol/L but <3.0 mmol/L, then further workup with an anion gap (serum chemistry) or pH (blood gas) can clarify the extent of metabolic derangement:

ii. If the anion gap is >14 or the pH is <7.3, then the procedure should be cancelled and the patient should be sent to the nearest emergency department or seen by an endocrinologist for further evaluation.

iii. If the anion gap is ≤14 or the pH is ≥7.3, then the procedure can continue as scheduled with close monitoring and early postoperative oral intake.

iii. If an anion gap or pH cannot be obtained, then the procedure should be rescheduled.

d. If the ketone level is ≥3.0 mmol/L (regardless of anion gap or blood pH), the procedure should be cancelled and the patient should be sent to the nearest emergency department or seen by an endocrinologist for further evaluation.

e. For hospitalized patients and procedures >4 hours in duration, a blood ketone level and/or anion gap should be repeated post procedure.