Euglycemic DKA in Patients Taking SGLT2 inhibitors

Key Articles

- *Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern with SGLT2 Inhibitors. Diabetes Care. 2015;38(9):1638-42.*
- *Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. Journal of Diabetes Investigation. 2016;7(2):135-138.*

Patient Presentation

29-year-old female with h/o difficult to control type-1 diabetes presents with nausea/vomiting and feeling "weak". She takes insulin at home for her diabetes and recently started dapagliflozin therapy under the direction of her endocrinologist. Vital signs are: AF, HR 120, BP 90/60, RR 30, SpO_2 99%. Physical exam is unremarkable except for a mildly tender epigastric area. Labs return with a VBG of 7.10, PCO2 of 22, and a LA: 3.1. K 6.1, AG 26, BHB 7.5. Patient was admitted to the ICU, her AG closed within 7-8 hours, but quickly reopened requiring an insulin infusion once again.

Background

- Common oral diabetic therapies used today:
  - Insulin sensitizers (Metformin)
  - Secretagogues (Sulfonylureas)
  - GLP-1 analogues
  - Gliptins
  - New Kid on the Block: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors
    - Gliflozins (Cana*gliflozin*, dapa*gliflozin*, etc.) – more commonly being prescribed as a 2nd line treatment.
- Recognized complications of oral DM treatments
  - Hypoglycemia, prolonged hypoglycemia
  - Lactic acidosis
  - Increase in reports of "Euglycemic DKA" as a result of SGLT-2 inhibitors

SGLT2 Inhibitors

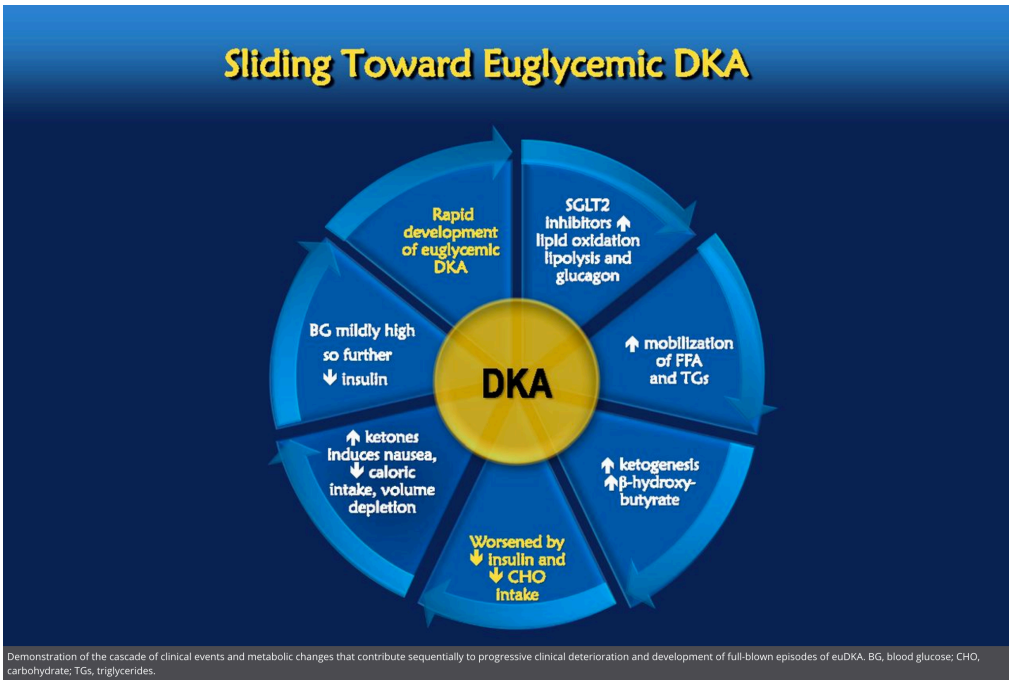
- **Mechanism**: Targets the SGLT2 receptors in the proximal renal tubules, preventing the reabsorption of glucose from urine, effectively causing glucose loss through urinary excretion.

- **Growth in frequency of use:** Over the past 5 years, there has been increased utilization of recently FDA approved sodium-glucose cotransporter 2 inhibitors for the outpatient management of Type 2 and in some cases, as an off-label adjunctive treatment for T1D
    - Based off of initial FDA studies of SGLT2i's, appeared to be a low risk medication where the risk of DKA was < 0.1%
    - **Favorable side effect profile:** An increase in reported (+) side effects including *less glucose variability, weight loss, and lower insulin doses* that has even made its way through social media outlets has increased consumer requests for the drug to be added to their DM regimen, even in T1D patients.

PEARL: Gliflozins are usually dosed daily, and usually have a half-life of 11-13 hours. As a result, effects are often prolonged especially in acute illness.

Euglycemic DKA in SGLT2i Use

- **Traditional DKA presentation:** In both T1D and T2D, DKA presents with marked hyperglycemia, typically > 350 mg/dL, glycosuria, metabolic acidosis, and hyperketonemia (BHB levels > 4)
- **Euglycemic DKA** is defined as DKA with a plasma GLU < 300 mg/dL, can happen in T1D but also in patients taking a SGLT2i.



- **Why SGLT2i's can cause ketoacidosis**
    - T2D patients have insulin, but increased urinary excretion of GLU and make the body turn to glycolysis and ketosis as a means for energy production
    - Home plasma GLU levels are often "normal"

    - Patients think will often decrease home sliding scale use, which will in turn increase glucagon release and ketogenesis.
- **Risk factors for development:**
    - Type 1 diabetics
    - Change in carbohydrate intake (starvation)
    - Recent surgery, New onset illness/increased metabolic stressor
    - Decreased home insulin administration
    - Alcohol use

Treatment

- Fortunately, the treatment of euDKA is very similar to standard DKA
- **Fluids:** Focus on IV fluid resuscitation first (SGLT2i's cause glucosuria and volume depletion)
- **Insulin:** Low dose insulin infusion often required to improve intracellular glucose utilization and reduce ketosis
- **D_5NS:** Concomitant dextrose infusion prevents hypoglycemia
- **Once patients taking SGLT2i's develop DKA, they are often permanently discontinued**

PEARL: Even if the anion gap closes, patients will often need to continue insulin infusion therapy for 24-hours, as SGLT2i's have a prolonged half-life.

Common side effects of other oral antihyperglycemic agents

Common Oral Antihyperglycemic Agents and Effects			
Mechanism	**Class**	**Common Drug Names**	**Side Effects**
"Secretagogues:" ↑ production of insulin by acting on pancreas; **can cause severe hypoglycemia**	Meglitinides	Repaglinide nateglinide	**Hypoglycemia**, short-acting (<4hrs)
	Sulfonylureas	Chlorpropamide glipizide, glyburide, glimepiride, gliclazide	**Hypoglycemia**, chlorpropamide: SiADH, disulfiram-like reaction
"Sensitizers": ↑ sensitivity to insulin	Biguanides	Metformin phenformin	**Lactic acidosis**, diarrhea, B_{12} deficiency
	Thiazolidinediones	Rosiglitazone, pioglitazone	Hepatotoxicity, heart failure exacerbation, ↑ fracture risk
↑ Insulin secretion (glucose dependent) ↓ glucagon	Glucagon-like peptide (GLP-1) analogues	Exenatide, liraglutide	Nausea, pancreatitis (exenatide)
Dipeptidyl peptidase-4 (DPP-4) inhibitors: ↑ GLP-1, ↑ insulin, ↓ glucagon	Gliptins	Sitagliptin (Januvia®), vildagliptin, saxagliptin	Upper respiratory infection symptoms, headache, acute pancreatitis (questionable)
α-Glucosidase inhibitors: ↓ carbohydrate digestion	Oligosaccharide	Acarbose, miglitol, voglibose	Hepatotoxicity, abdominal cramping, diarrhea
SGLT-2 inhibitors: blocks Na-glucose co-transporter 2	Gliflozins	Canagliflozin (Invokana®), dapagliflozin	**Euglycemic DKA**, orthostasis, urinary tract infections, mycotic infections (balanitis, vaginitis), ↑ K^+

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