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An Unusual Case of Severe Metabolic Acidosis in MICU: SGLT2 Inhibitor-Associated Diabetic Ketoacidosis

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HCA | Graduate Medical Education

Patient Presentation

51-year old female presented to the emergency department (ED) for a four day history of nausea, vomiting and generalized weakness

-Lower chest pain x 1 day, worsen by deep breath

-Diffuse abdominal pain

-Denies fever, chills, cough, diarrhea, dysuria

-No recent history of recent travel or ingestion of toxic substances

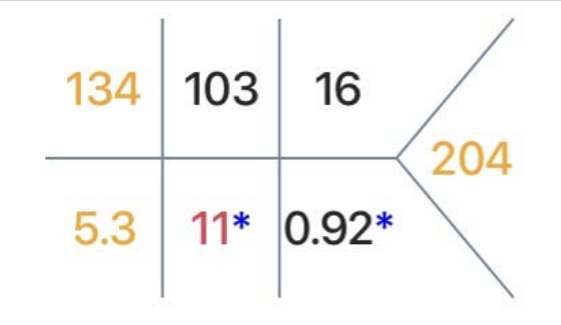
- **Past medical history/past surgical history**
  - Type 2 diabetes mellitus / obesity class 3 BMI 53 / hypertension / restless syndrome
  - Cholecystectomy/abdominal hernia repairsx2
- **Home Medications**
  - Empagliflozin (SGLT2 inhibitor)
  - Dulaglutide
  - Insulin glargine
  - Others: atorvastatin, trazodone, ropinirole, losartan
- **Family / Social history**
  - Father has HTN, CAD s/p CABG in 60's
  - Denies alcohol use, tobacco use or recreational drug us

Physical Exam

Vitals: Temperature 36.7 ℃, heart rate 101 beats/min, blood pressure 135/89 mmHg, respiration rate 24 breaths/min and oxygen saturation 97% on room air

General appearance: obese, alert, awake, oriented
Head/Eyes: atraumatic, clear cornea, normal conjunctiva/sclera
ENT: dry mucosal membrane, normal pharynx
Neck: supple/no meningismus, no bruit/NL carotids
Cardiovascular: normal capillary refill, normal heart sounds, regular rate and rhythm, normal S1/S2
Respiratory: deep and labored breathing, chest symmetric expansion, no tenderness, clear to auscultation,
Abdomen: soft, non-tender, normal bowel sounds
Genitourinary: no flank pain, no foley
Extremities: moves all, normal capillary refill
Musculoskeletal: normal inspection
Neuro/CNS: alert, oriented X 3, normal speech
Skin: normal color, normal temperature
Psychiatry: normal affect, normal judgment/insight, normal mood

Clinical Data



Other pertinent labs:

- Small serum acetone
- Large urine ketones
- Lactic acid 1.3 mg/dL
- Anion Gap: 20 meq/L
- “Delta-Delta” ratio 0.57

Test	Value	Norm Range
ABG PH	7.08 CL	7.35-7.45 pH
ABG PCO2	24 L	35-45 mmHg
ABG PO2	112 H	80-100 mmHg
ABG HCO3	6.9 L	22-26 meq/L
ABG BE	-22 L	-2-2 MMOL/L

Other pertinent labs:

- Measured serum osmolality 304
- Calculated serum osmolality 287
- Osmolality gap 17
- Serum alcohol <3 mg/L
- B-hydroxybutyrate not available at early phase of assessment and treatment

Hospital Course

Emergency team

- 0.9% saline 2 liters

Hospital medicine team

- Initiated bicarb drip
- Ordered insulin drip
- Consulted Critical Care team

Critical Care team

- Euglycemic diabetic ketoacidosis (DKA) secondary to fatal SGLT2i-induced DKA was highly suspected
- DKA standard of care was initiated with:
  - Intravenous insulin
  - Intravenous fluid
  - Bicarb drip
  - Electrolyte disturbance correction
- ICU course
  - After twenty-eight hours, the patient's anion gap normalized and intravenous insulin was discontinued

	28HR	10HR	2HR
ABG PH	7.45	7.13 CL	7.08 CL
ABG PCO2	44	25 L	24 L
ABG PO2	76 L	115 H	112 H
ABG HCO3	30.0	8.2 L	6.9 L
ABG BE	5 H	-19 L	-22 L
ABG TCO2	31.0 H	9.0 CL	8.0 CL
ABG O2SAT	96	97	96
Anion Gap	12	22	20
HCT %	36.5	46.4	54.4

Atypical DKA in this case

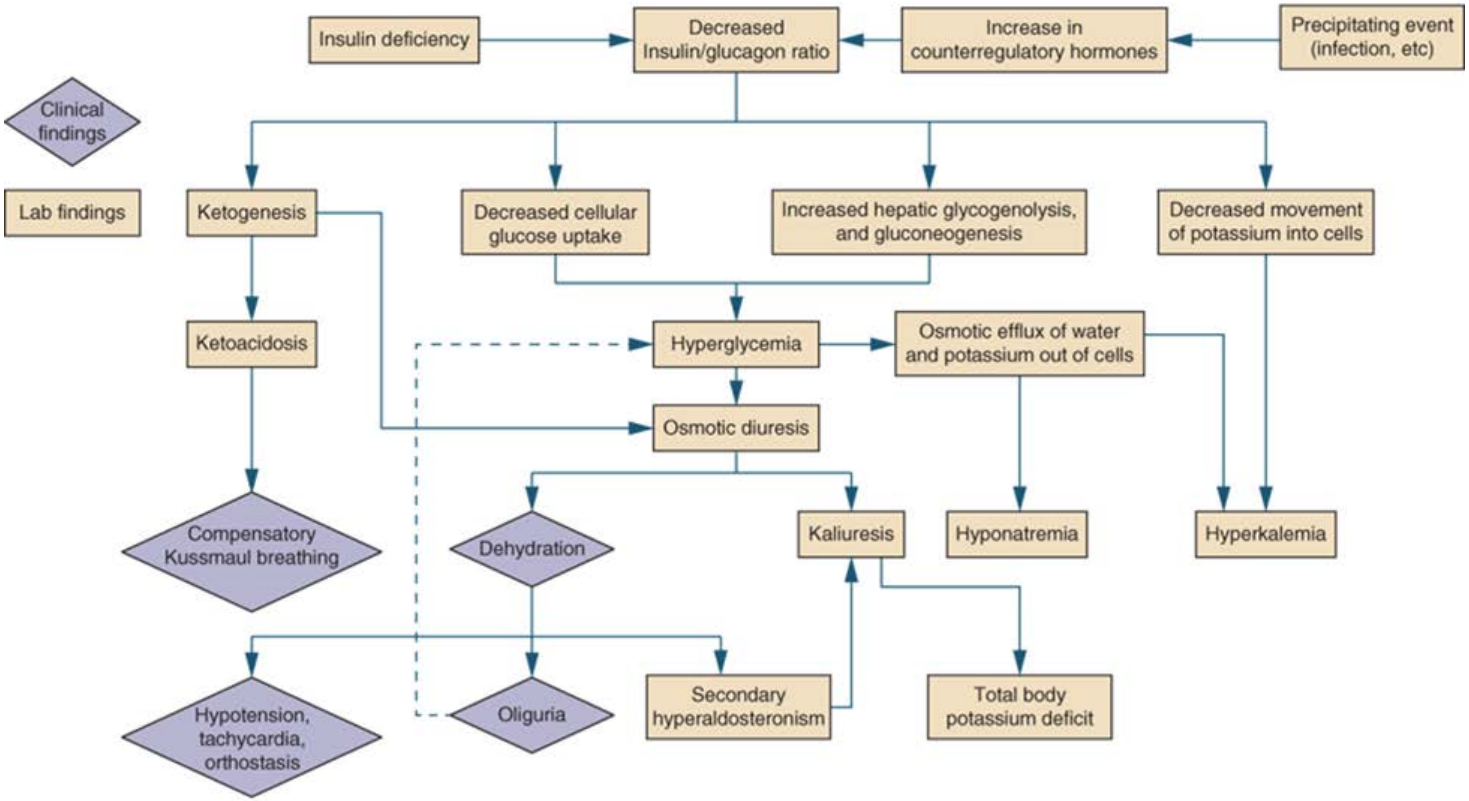
- Severe metabolic acidosis
- Near normal serum glucose level
- Very small serum acetone
- B-hydroxybutyrate result not available during initial assessment

At a later date after the patient was discharged home, B-hydroxybutyrate result returned

73 mg/dL (normal 0.2-2.8 mg/dL)

DKA Pathophysiology

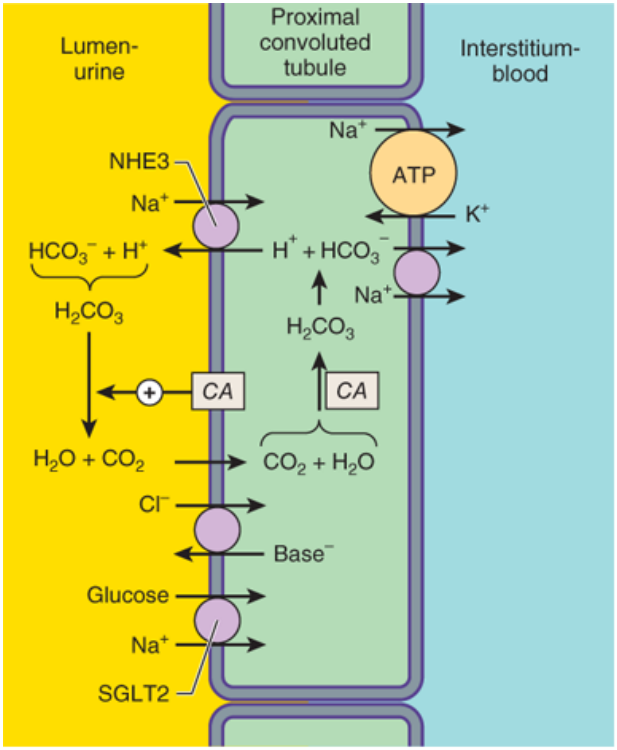
- DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone).
  - Both insulin deficiency and glucagon excess are necessary for DKA to develop.



Powers AC, Niswender KD, Rickels MR. Diabetes Mellitus: Management and Therapies. *Harrison's Principles of Internal Medicine, 20e* New York, NY: McGraw-Hill

SGLT2 Inhibitor

- SGLT-2 receptor is responsible for 90% of the active glucose reabsorption of the kidney's proximal tubule.
  - By inhibiting this receptor, glucose reabsorption is decreased.
  - Glucose passes into the urine, serum glucose is lowered
- Renal tubular cells from T2DM patients show increased levels of SGLT2, thereby offering a mechanism by which the kidney of a patient with DM achieves its increased ability for glucose reabsorption.



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Euglycemic DKA

- Mechanism:
  - decreased *release* of insulin (due to the lower glucose levels)
  - direct stimulation of glucagon release, and ketogenic effects
- Risk may be higher in:
  - patients undergoing stressful events, such as surgery.
  - with concurrent insulin use
  - patients with lower insulin levels, such as LADA (latent autoimmune diabetes of the adult).
- Due to glucosuria, DKA in these patients is often associated with near normal glucose levels

Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1687-1693.

Mechanisms for Euglycemic DKA

Donnan JR, et al, BMJ Open. 2019 Feb 1;9(1):e022577.
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Yu X, et al. *Int J Endocrinol.* 2018;2018:7074868.

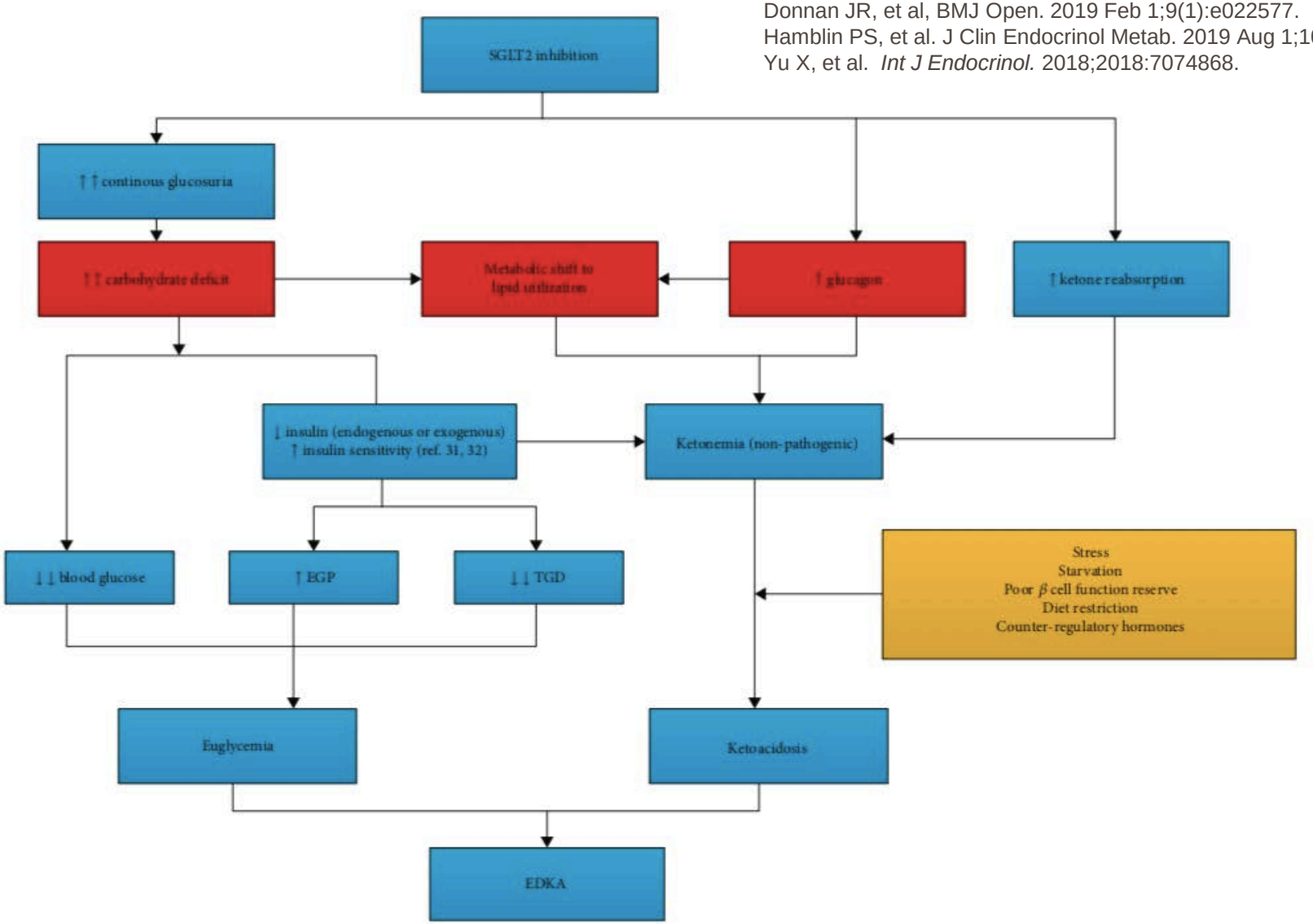

FIGURE 2: Pathogenesis of SGLT-2 inhibitor-associated EDKA. EGP: endogenous glucose production; TGD: tissue glucose disposal.

Approach to Better Practice

Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. *Diabetes Care.* 2015;38(9):1638-1642

- Clinical manifestations
  - This type of DKA can be easily missed. Clinicians need to improve awareness to quickly recognize and treat this condition early as it can be fatal.
    - ✓ DKA can occur in the setting of relative euglycemia
    - ✓ Vigilance for patients with acidosis
- Testing
    - ✓ Promptly evaluate for urine and/or plasma ketones, any time a SGLT2 inhibitor–treated patient feels unwell regardless of the glucose levels
    - ✓ Urine and/or plasma acetone not enough, sometimes plasma acetone normal
    - ✓ **Always check B-hydroxybutyrate**
- Treatment
    - ✓ Discontinue the offending medication
    - ✓ DKA standard management

Questions

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