Euglycemic DKA

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Endorama, 2/27/25

Objectives

1. Discuss the evaluation of and differential diagnosis for euglycemic diabetic ketoacidosis (DKA).
2. Review clinical factors and common scenarios which increase risk for euglycemic DKA.
3. Show how anticipating and correctly diagnosing euglycemic DKA is highly relevant and important to patient safety.

Case

- **71-year-old female** with invasive rectal cancer treated with FOLFOX, type 2 diabetes, CKD3 with severe proteinuria and secondary hyperPTH, hypothyroidism.
- Planned for **abdominoperitoneal resection of rectal cancer**. She was admitted 1 day early because of a fall in the shower, and it was deemed reasonable to proceed with the planned surgery.
- **Diabetes history**: diagnosed in her 30s, no GDM. Mother with DM, current BMI 21.
- **Diabetes regimen** while off steroids from chemotherapy:
  - Glargine 5 units once daily.
  - Lispro 5 units with meals.
  - Dapagliflozin 10 mg daily.
- AGP from CGM shows a **GMI of 7.5%.**
- **Preop labs**: CO2 20, AG 13, Cr 1.27 (eGFR 45, BL ~1.0), no BHB sent.

Case: Post-operative course

- **POD #0**: Abdominal peritoneal resection with creation of myocutaneous flap and colostomy, performed by CRS and PRS without complication.
- **POD #1**: Endocrinology consulted, she was seen by Dr. Abe, her outpatient endocrinologist, and Dr. Jain who recommended:
  - Continuing glargine 5 units once daily and MDSSI Q4 hours given the patient was NPO with evolving plan for her nutrition.
  - Holding dapagliflozin inpatient and resuming on discharge.
- She did not receive any doses of dapagliflozin in the hospital, and it was taken off her medication list at her Anesthesia pre-op visit 1 week prior to admission.

Case: Post-operative course

- **POD #1**: NPO, awaiting return of bowel function
- **POD #2**: NPO, awaiting return of bowel function
  AKI noted on labs to Cr 1.64
- **POD #3**: return of bowel function noted, advanced to CLD
- **POD #4**: advanced to low-fiber diet; later made NPO again after emesis and KUB showing moderate ileus
- **POD #5**: decision to pursue TPN
- **POD #6**: KUB improved, started PPN instead and advanced to CLD
  AKI noted to be persistent with Cr 1.4, AG 22, CO2 12, serum ketones 5.04
  BG 185 (range 102-185 over the last 24 hours)

Transferred to SICU due to concern for euglycemic DKA

Is this euglycemic DKA?

Summary:

- She's now **POD #6** on PPN with limited oral intake and fluids since surgery
- Labs show: Cr 1.4 (BL 1.0), AG 22, CO2 12, serum ketones 5.04
- BG 185 (range 102-185 over the last 24 hours)

Euglycaemic Diabetic Ketoacidosis

J. F. MUNRO, I. W. CAMPBELL, A. C. McCUISH, L. J. P. DUNCAN

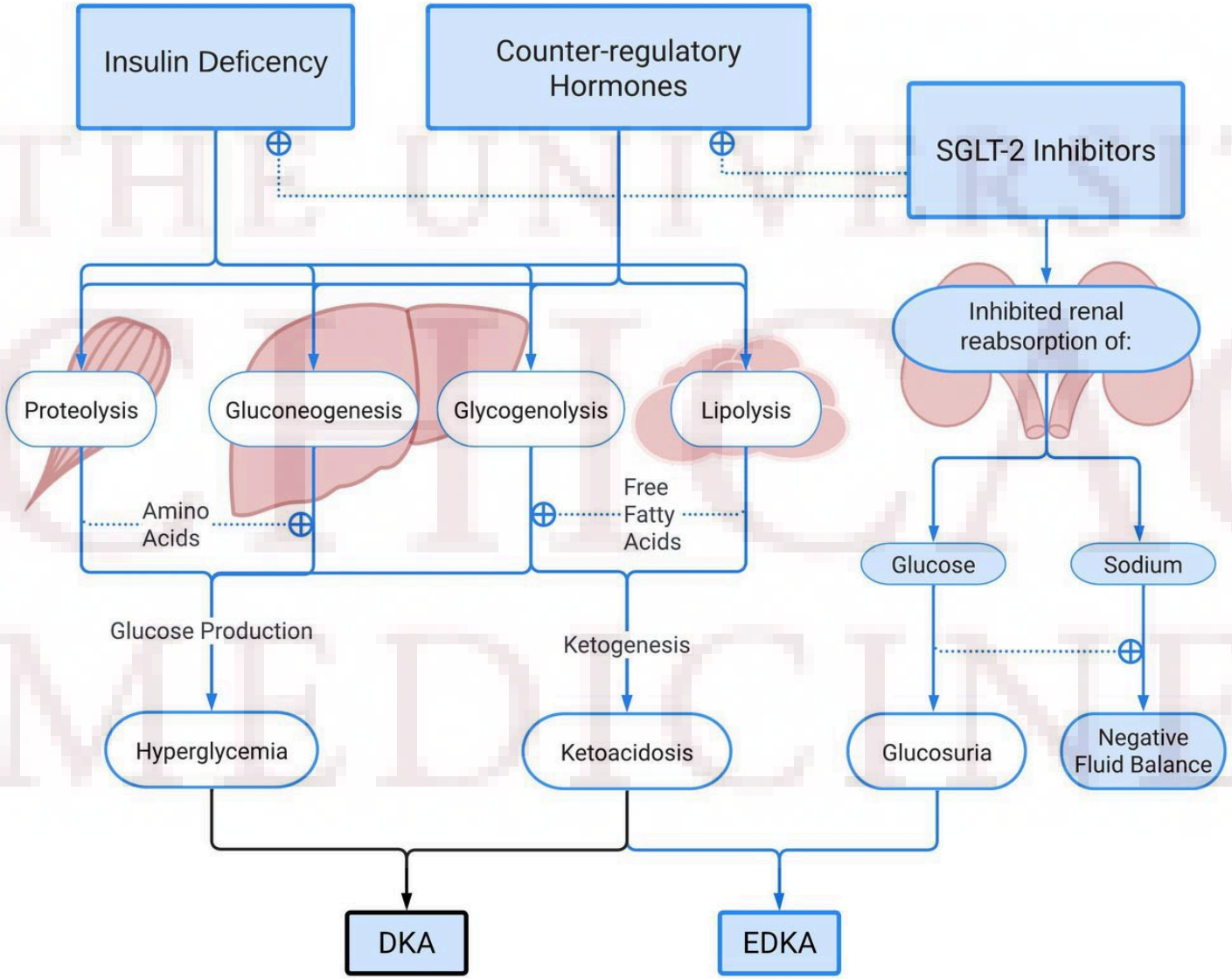
British Medical Journal, 1973, 2, 578–580

No SGLT2 inhibitors

Summary

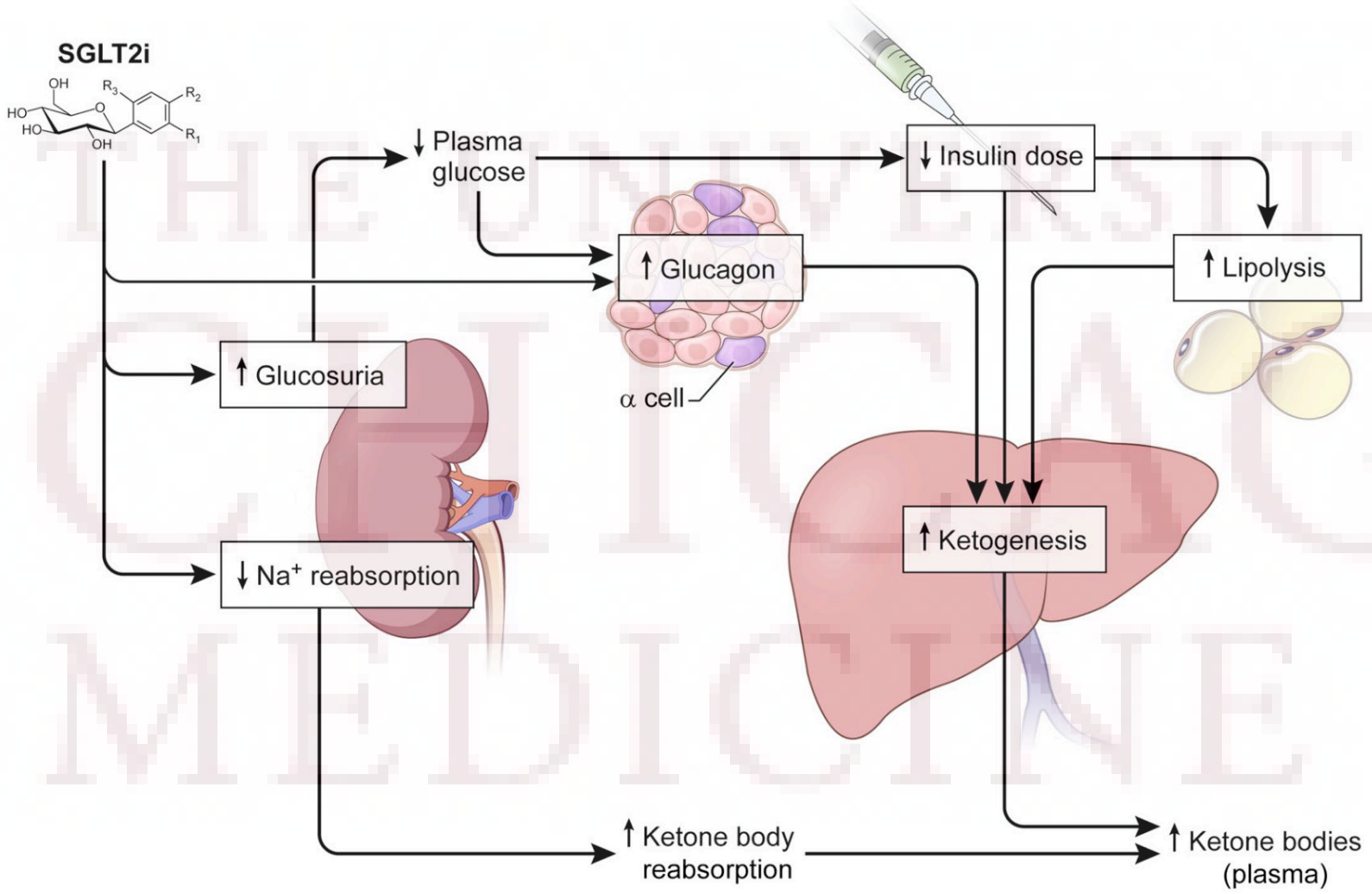
Of a series of 211 episodes of diabetic metabolic decompensation 37 had severe euglycaemic ketoacidosis (a blood sugar level of less than 300 mg/100 ml and a plasma bicarbonate of 10 mEq/l. or less). All were young insulin-dependent diabetics, only one being previously undiagnosed. Vomiting was a common factor, and in all carbohydrate reduction occurred with continued or increased daily insulin dose. Treatment comprised fluid and electrolyte replacement and large doses of insulin covered by adequate carbohydrate, many receiving 10% dextrose. Alkali was either withheld or given sparingly and the therapy was monitored by serial estimations of plasma bicarbonate. All the patients survived.

Pathophysiology of ketosis and DKA



Chow et al. BMJ Open Diab Res Care. 2023 Oct;11(5):e003666.

SGLT2 inhibitors and ketosis



Taylor et al. JCEM. 2015 Aug;100(8):2849–52.

Evaluating potential euglycemic DKA

- **History**: Detailed history focusing on SGLT2 inhibitor use as well as other causes of ketosis with or without elevated AG.
- **Labs:** BG can be <200 mg/dl. BMP and serum ketones are usually sufficient as an initial evaluation and would show elevated AG and ketosis. Urinalysis can show glycosuria which could be consistent with SGLT2 inhibitor use versus hyperglycemia (however RGT is >200 mg/dl).
- **Differential:** stress or illness, starvation, alcohol use, ingestion (methanol, polyethylene glycol, salicylates, TCAs), renal failure, lactic acidosis.

Euglycemic DKA is a **diagnosis of exclusion** requiring **high clinical suspicion**

Chow et al. BMJ Open Diab Res Care. 2023 Oct;11(5):e003666.

Diagnostic criteria for DKA

DKA	**A. DKA Diagnostic Criteria**	
	Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) OR prior history of diabetes
	Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L OR urine ketone strip 2+ or greater
	Metabolic Acidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L
HHS	**B. HHS Diagnostic Criteria**	
	Hyperglycemia	Plasma glucose ≥600 mg/dL (33.3 mmol/L)
	Hyperosmolarity	Calculated effective serum osmolality >300 mOsm/kg (calculated as [2xNa⁺ (mmol/L) + glucose (mmol/L)]), OR total serum osmolality >320 mOsm/kg [(2xNa⁺ (mmol/L) + glucose (mmol/L) + urea (mmol/L)]
	AbSence of significant ketonemia	β-Hydroxybutyrate concentration <3.0 mmol/L OR urine ketone strip less than 2+
	Absence of acidosis	pH ≥7.3 and bicarbonate concentration ≥15 mmol/L

Umpierrez et al. Diabetes Care. 2024 Jun 22;dci240032.

Risk factors for euglycemic DKA

- **Medications**: SGLT2 inhibitor use
- **Insulin deficiency**: Missed insulin doses, insulin pump failure, missed diagnosis of T1D or LADA
- **Drug use**: Alcohol use, cocaine
- **Starvation**: Anhedonia, anorexia, low BMI, ketogenic diet, dehydration, persistent vomiting, gastroparesis
- **Physiologic stress or illness**: Infection, sepsis, surgery, extreme exertion, trauma, acute pancreatitis, chronic liver disease, pregnancy

Chow et al. BMJ Open Diab Res Care. 2023 Oct;11(5):e003666.

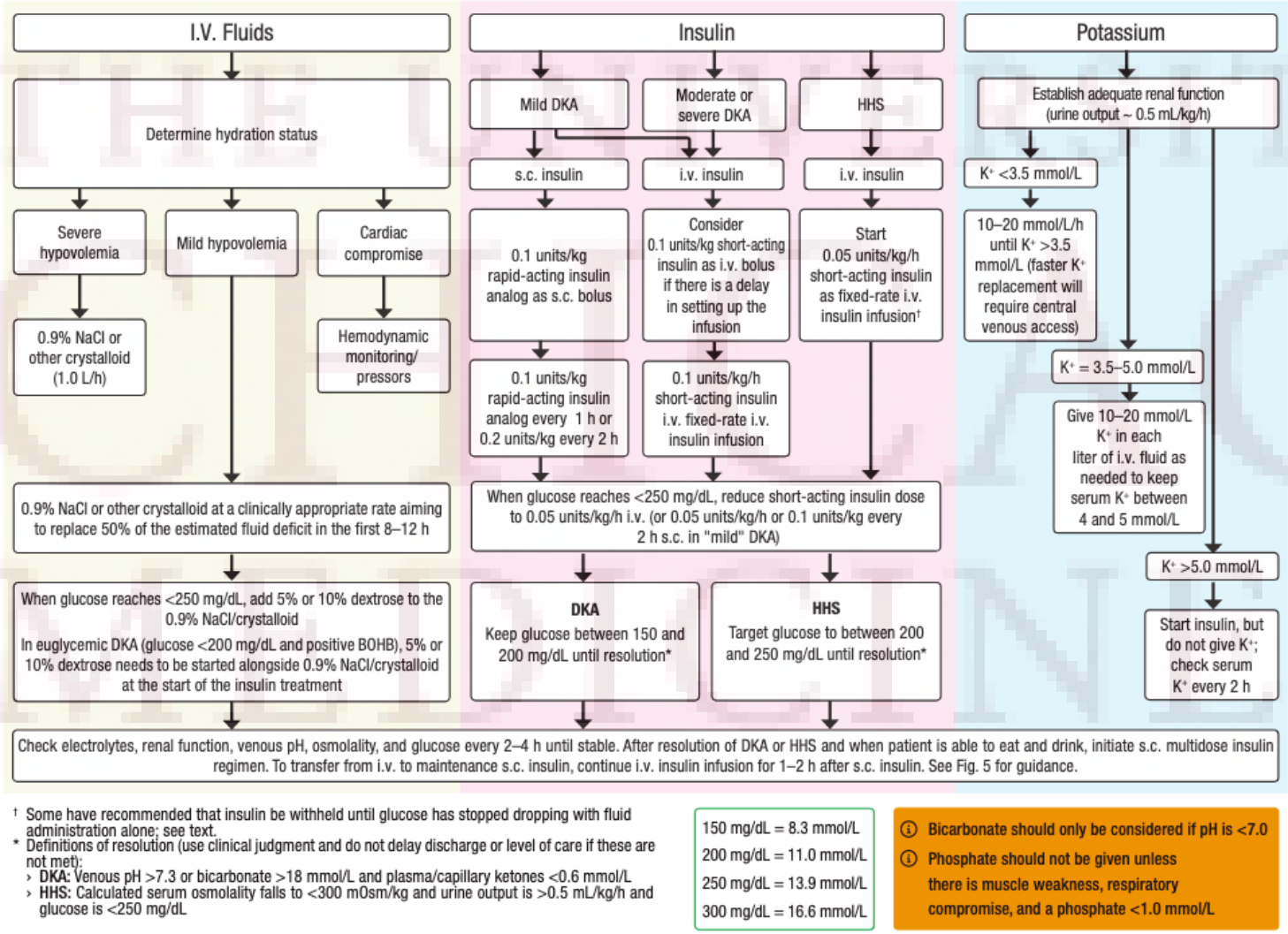
What would you recommend for management of our patient?

As a reminder:

- She's now **POD #6** on PPN with limited oral intake and fluids since surgery
- Labs show: Cr 1.4 (BL 1.0), AG 22, CO2 12, serum ketones 5.04
- BG 185 (range 102-185 over the last 24 hours)

SICU wants to know if they should start an insulin drip (!)

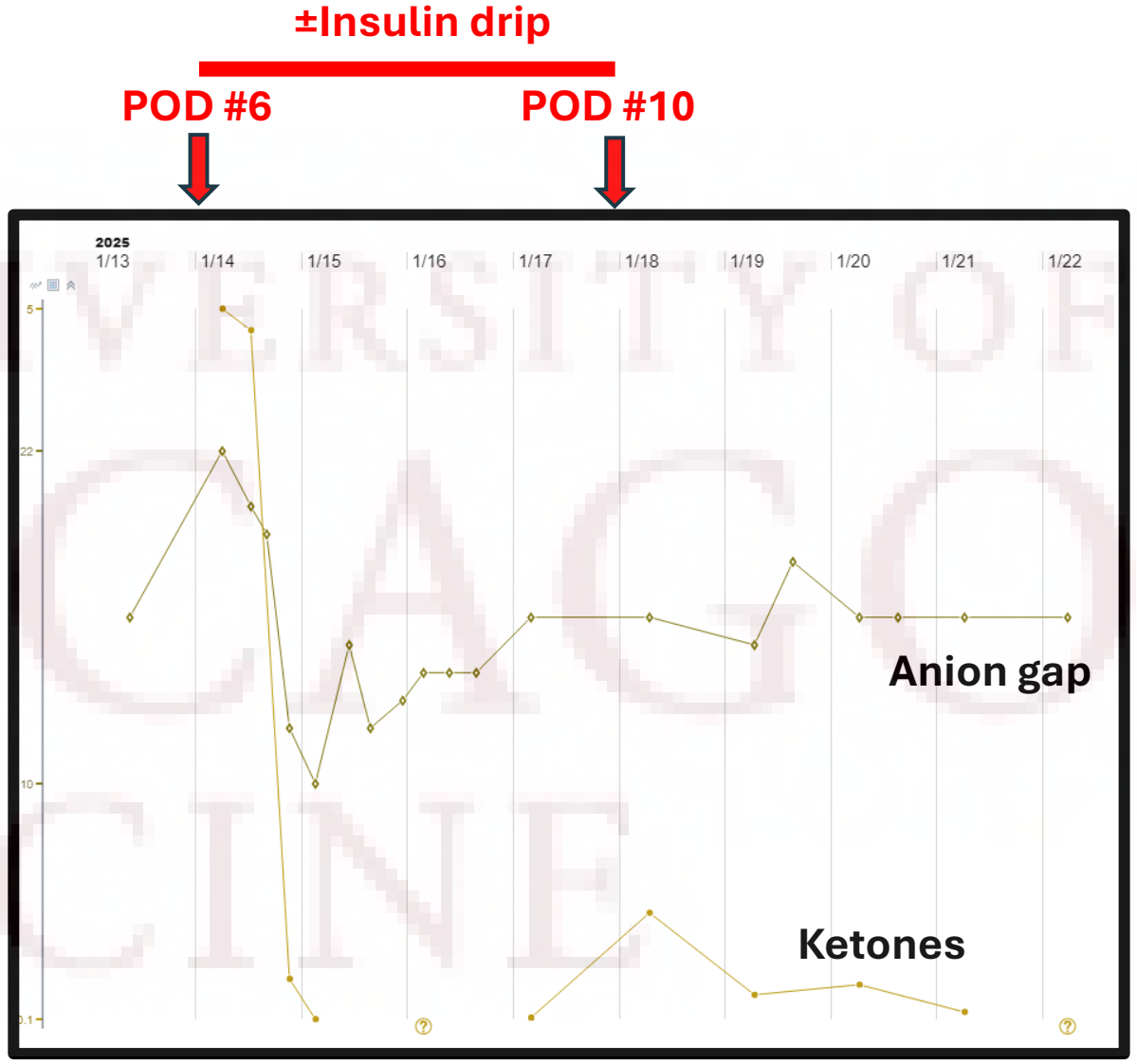
Management of euglycemic DKA



Umpierrez et al. Diabetes Care. 2024 Jun 22;dci240032.

Case: Update

- Her AG closed with insulin drip intermittently through **POD #9**
- She transitioned to low-dose glargine with LDSSI and transferred back to the floor on **POD #10**
- She was started on TPN after improvement of her ketosis as the GI Nutrition team was not comfortable starting due to the concern for euglycemic DKA
- TPN was stopped later in her hospital course and she was transitioned to nutrition by mouth before discharge

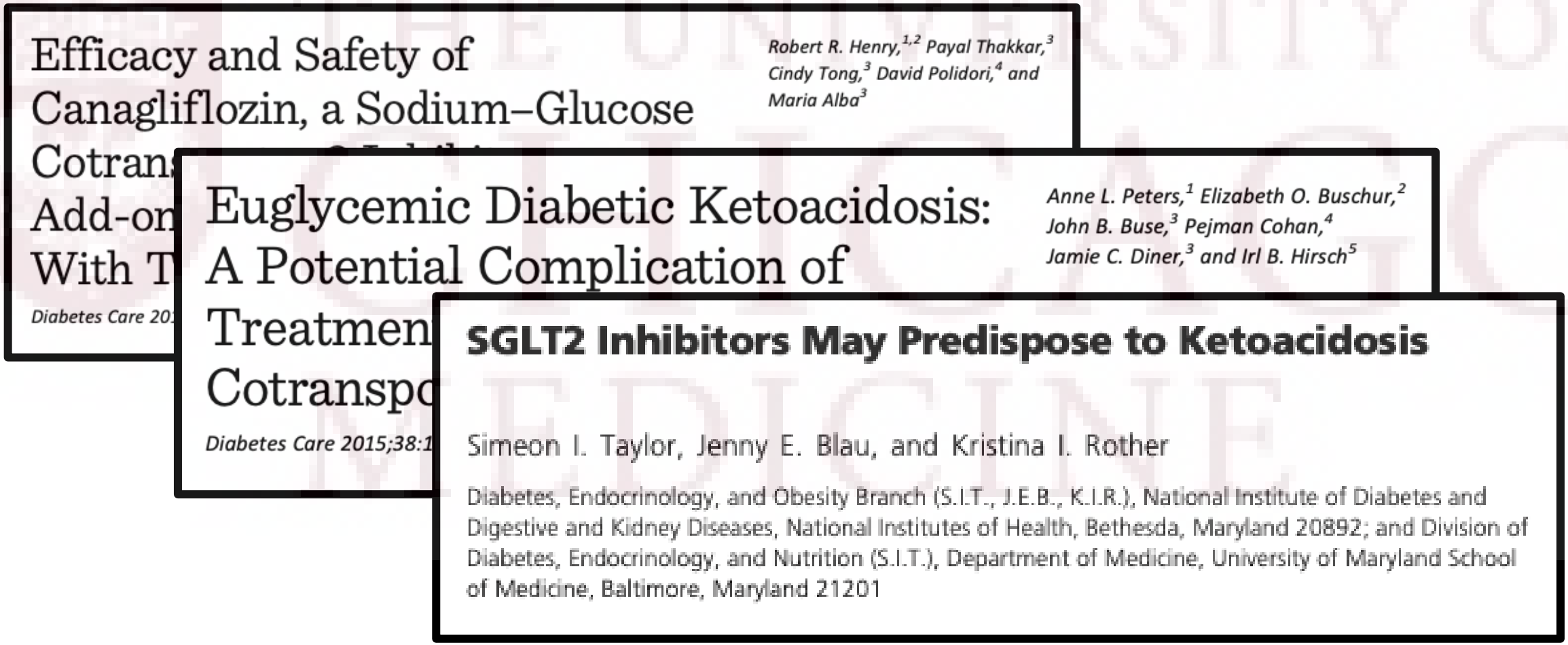


SGLT2 inhibitors and euglycemic DKA: FDA revision of labels in 2015

FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections

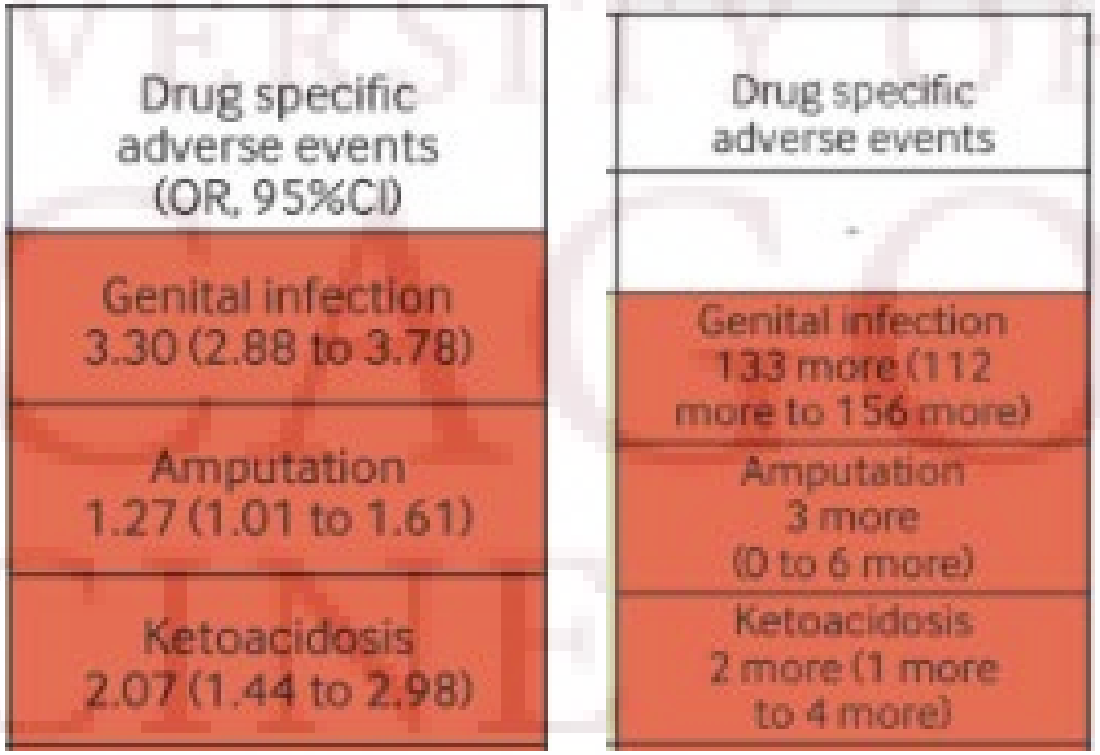
This communication provides updated information to the FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood issued on May 15, 2015.

SGLT2 inhibitors and euglycemic DKA: Building evidence in 2015



SGLT2 inhibitor treatment increases risk of ketoacidosis in meta-analysis of 816 trials

- Systematic review and meta-analysis by Shi et al
- 816 trials with 471,038 patients comparing antihyperglycemics for T2D, including SGLT2 inhibitors
- Confirmed increased risk of DKA with SGLT2 inhibitor use, but look at absolute risk



This rate is compared to 1,000 patients over 5 years of standard treatments

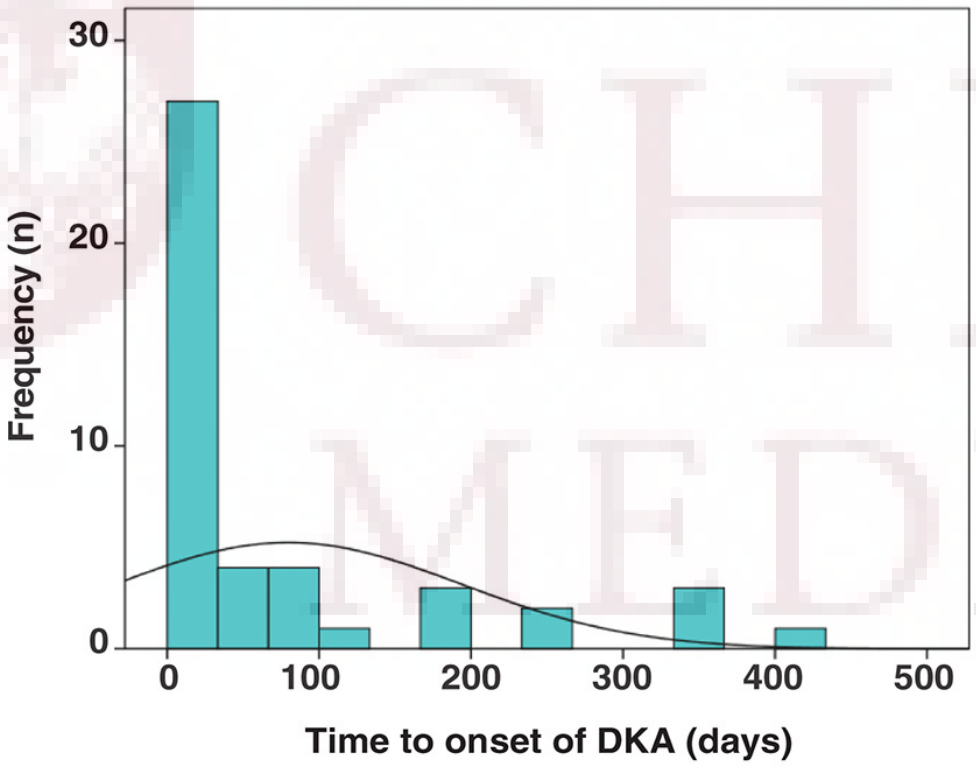
Shi et al. BMJ. 2023 Apr 6;e074068.

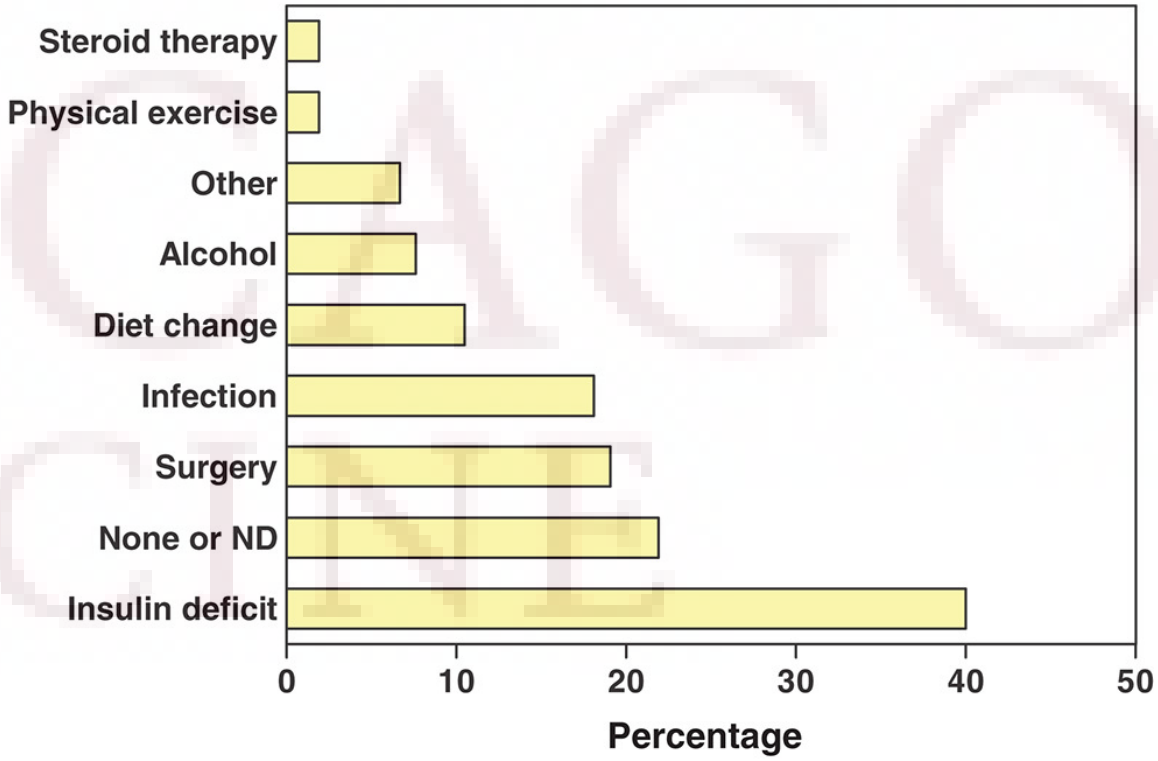
Which SGLT2 inhibitor poses highest risk?

Study Group	Patients, n*	Events, n	Person-Years	Crude IR (95% CI)†	Crude HR (95% CI)	Adjusted Model HR (95% CI)
SGLT-2 inhibitors	202 186	372	183 374	2.03 (1.83-2.25)	2.83 (1.93-4.14)	2.85 (1.99-4.08)
DPP-4 inhibitors	202 186	133	177 615	0.75 (0.63-0.89)	Reference	Reference
Canagliflozin	78 779	200	88731	2.25 (1.96-2.59)	3.65 (2.06-6.48)	**3.58 (2.13-6.03)**
DPP-4 inhibitors	78 779	58	87 125	0.67 (0.51-0.86)	Reference	Reference
Dapagliflozin	36 746	58	28 528	2.03 (1.57-2.63)	1.87 (1.12-3.13)	**1.86 (1.11-3.10)**
DPP-4 inhibitors	36 746	32	27 187	1.18 (0.83-1.66)	Reference	Reference
Empagliflozin	26 728	25	16 970	1.47 (1.00-2.18)	2.32 (1.14-4.72)	**2.52 (1.23-5.14)**
DPP-4 inhibitors	26 728	11	17 575	0.63 (0.35-1.13)	Reference	Reference

Douros A et al. Ann Intern Med. 2020 Sep 15;173(6):417–25.

Risk highest at SGLT2 inhibitor initiation





Bonora BM et al. Diabetes, Obesity and Metabolism. 2018 Jan;20(1):25–33.

Mitigating risk of SGLT2 inhibitor use

- Hold SGLT2 inhibitors prior to surgery based on guidance from the FDA and multiple societies, including ADA Standards of Care 2025:

  SGLT2 inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (85–88). […] It is recommended that ***SGLT2 inhibitors should be stopped 3 days before scheduled surgeries*** *(4 days for ertugliflozin) (89).*

- Careful prescription of SGLT2 inhibitors in light of risk factors for DKA
- Reducing insulin doses cautiously when starting SGLT2 inhibitor
- Informing patients about the risk of SGLT2 inhibitor-associated DKA, including when to withhold an SGLT2 inhibitor, including acute illness with reduced oral intake, symptoms of DKA, and providing return precautions

Milder TY et al. Drug Saf. 2020;43(12):1211–21.

Would you stop her SGLT2 inhibitor on discharge?

Relevant updates:

- She's now back on the floor with good oral intake
- Her AG is no longer elevated and serum ketones are suppressed
- She has a stable inpatient insulin regimen without dapagliflozin

The primary team asks if she should continue SGLT2 inhibitor on discharge

Case: Resolution

- It was never clear whether she took dapagliflozin prior to surgery but her dispense records suggest she had not
- Most likely her presentation was caused by a combination of surgical stress and starvation ketosis
- Her diabetes regimen on discharge **POD #14** was glargine 5 units once daily, LDSSI, and dapagliflozin 10 mg daily
- She had close follow-up in our clinic and was doing well, eventually resuming her mealtime insulin as well

dapagliflozin propanediol

	Dispensed	Days Supply	Quantity
FARXIGA 10MG TABLETS	01/22/2025	30	30 each
FARXIGA 10MG TABLETS	06/11/2024	90	90 each
FARXIGA 10MG TABLETS	02/29/2024	90	90 each
FARXIGA 10MG TABLETS	10/16/2023	90	90 each

Summary: Euglycemic DKA

- **Presentation.** Symptoms of DKA, elevated AG and ketosis in the absence of frank hyperglycemia (BG <200).
- **SGLT2 inhibitors:** Significant increase in risk, however, euglycemic DKA can occur without SGLT2 inhibitor use.
- **Additional risk factors**: Relative or absolute insulin deficiency, alcohol use, starvation, and physiologic stress.
- **Acute management**: Same as DKA and requires IV insulin, fluids, and carbohydrate replacement with close monitoring.
- **Patient counseling**: Euglycemic DKA while on SGLT2 inhibitor treatment should merit careful, individualized discussion regarding continuation of SGLT2 inhibitor therapy.

Acknowledgements

- Dr. Rajesh Jain
- Dr. Caroline Abe

What’s your approach to euglycemic DKA and SGLT2 inhibitor use?

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