

SGLT2-i and Euglycemic DKA

Adam Betz, MD
Medical Director, CV Critical Care/ECMO
Oklahoma Heart Institute
Tulsa, OK

Disclosures

- I am a speaker and advisory board member for Abiomed/J&J MedTech



Objectives

- Describe the presentation and pathophysiology of classic DKA
- Review the SGLT-2i medication class and its effects on glucose and insulin metabolism
- Describe the presentation and pathophysiology of euglycemic DKA, especially as relates to SGLT-2i
- Discuss the diagnosis and treatment of euglycemic DKA



Diabetic Subtypes

- **Type 1DM**
 - Hyperglycemia via absolute insulin deficiency
 - Requires exogenous insulin administration
- **Type 2DM**
 - Hyperglycemia secondary to insulin resistance
 - Patient *hyperinsulinemic* at baseline



Acute Hyperglycemic Complications of DM

- **Diabetic Ketoacidosis**
 - Moderate hyperglycemia
 - Ketosis
 - Acidosis
 - Inadequate insulin to stay out of lipolysis and ketosis
- **Hyperosmolar Hyperglycemic State**
 - Severe hyperglycemia
 - Increased hyperosmolality
 - Minimal ketosis
 - Minimal acidosis
 - Adequate insulin to keep out of lipolysis and ketosis



Diabetic Ketoacidosis

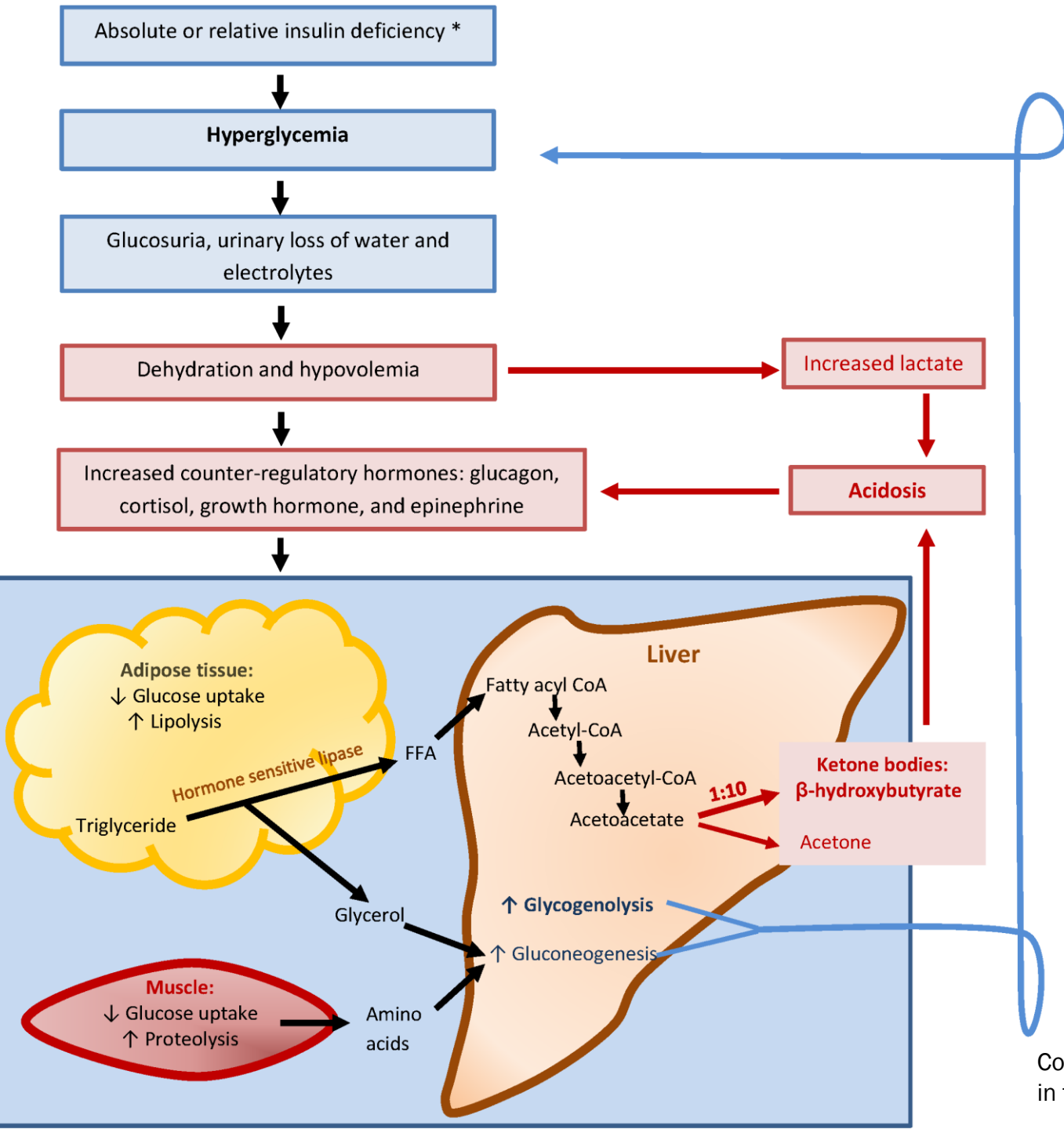
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- Hyperglycemia
 - Ketosis
 - Anion Gap Metabolic Acidosis



Diabetic Ketoacidosis



- **Commonly associated with type 1 DM**
 - Hyperglycemia secondary to absolute *insulin deficiency*
 - Increased counter-regulatory hormone response
 - Glucagon, growth hormone, catecholamines, corticosteroids.
 - Gluconeogenesis, proteolysis → hyperglycemia
 - Glycogenolysis, lipolysis → ketosis
- **Possible in type 2 DM (Increasingly possible...)**



DKA Pathophysiology

Cohen, M., Shilo, S., Zuckerman-Levin, N., & Shehadeh, N. (2015). Diabetic Ketoacidosis in the Pediatric Population with Type 1 Diabetes. InTech. doi: 10.5772/60592

Signs and Symptoms

- Nausea
- Vomiting
- Fatigue
- Anorexia
- Tachypnea
- Tachycardia
- Abdominal pain



Diabetic Ketoacidosis Diagnosis



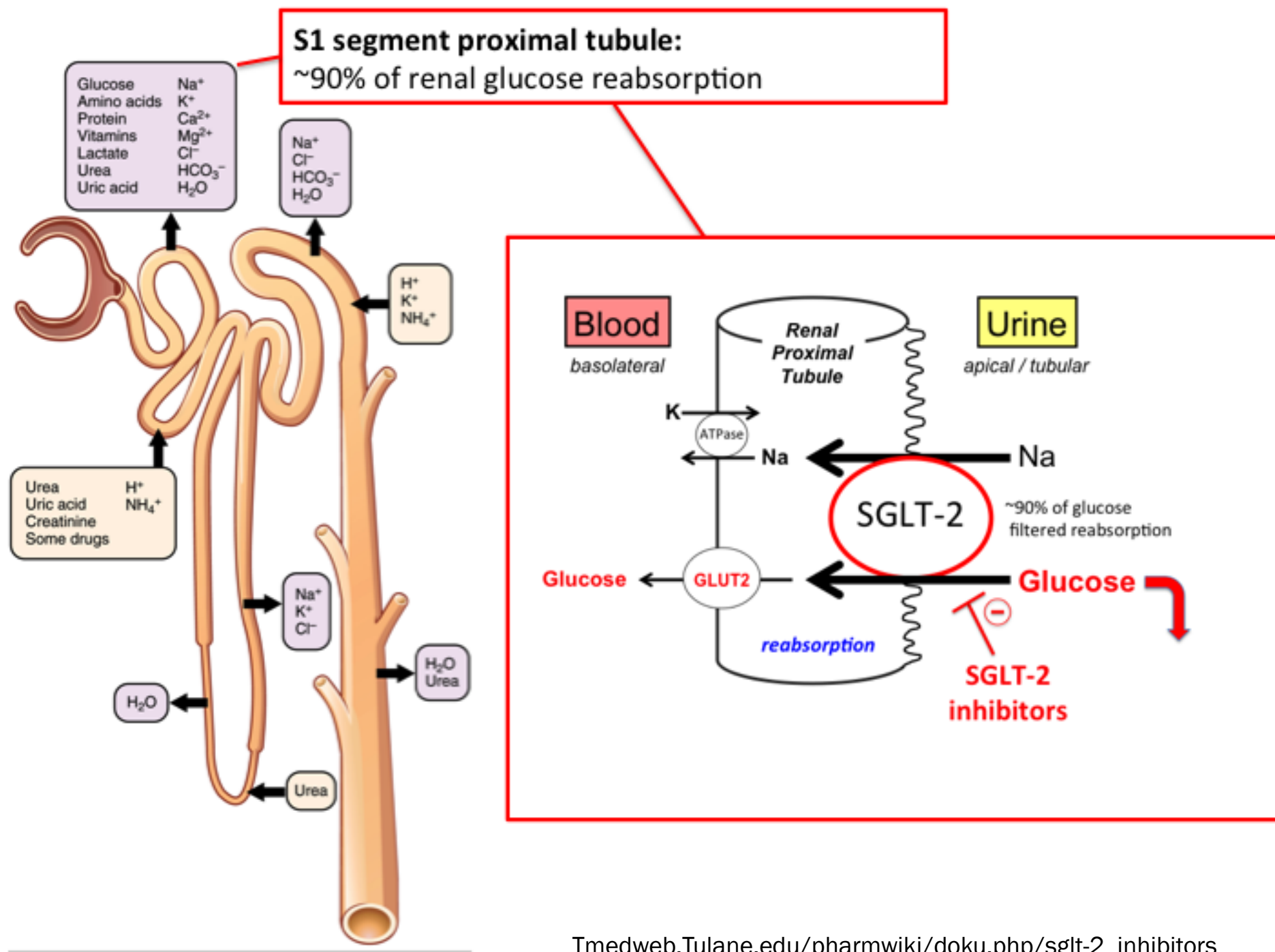
- **D:** glucose ≥ 200 mg/dL or prior history of diabetes
- **K:** Ketosis
 - Beta-hydroxybutyrate level ≥ 3 mmol/L or
 - Urine ketones 2+ or higher
- **A:** Metabolic acidosis
 - pH < 7.3 or
 - Bicarbonate concentration < 18 mmol/L or
 - Both of the above

SGLT-2 Inhibitors

- *Canagliflozin*
- *Dapagliflozin*
- *Empagliflozin*
- Ertugliflozin
- Bexagliflozin
- Sotaflozin



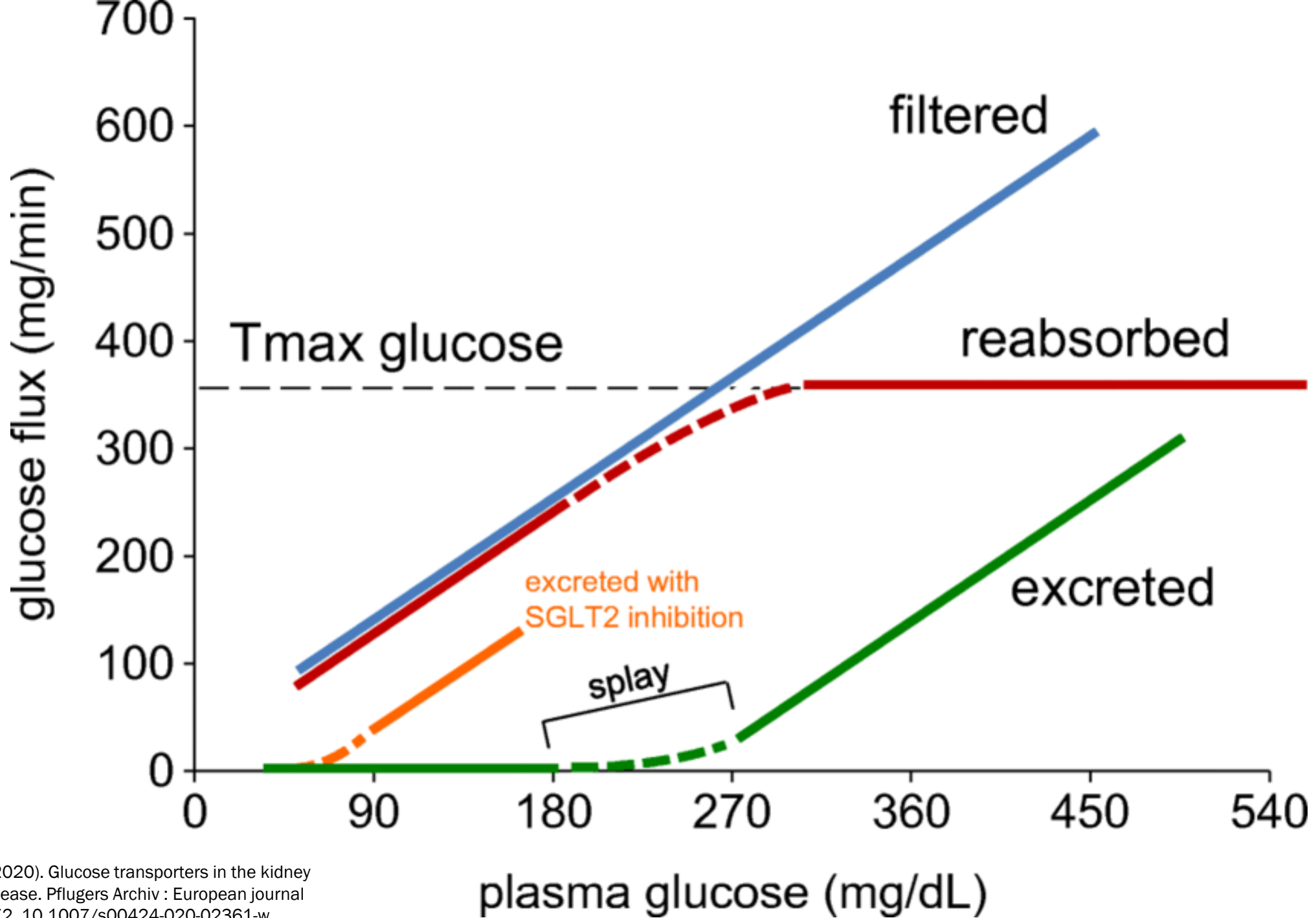
SGLT-2i



SGLT-2 Inhibitor Benefits



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- Improved glucose control in T2DM
 - Improve long term outcomes in HFrEF
 - Decreased major adverse cardiovascular events
 - Slow progression of CKD



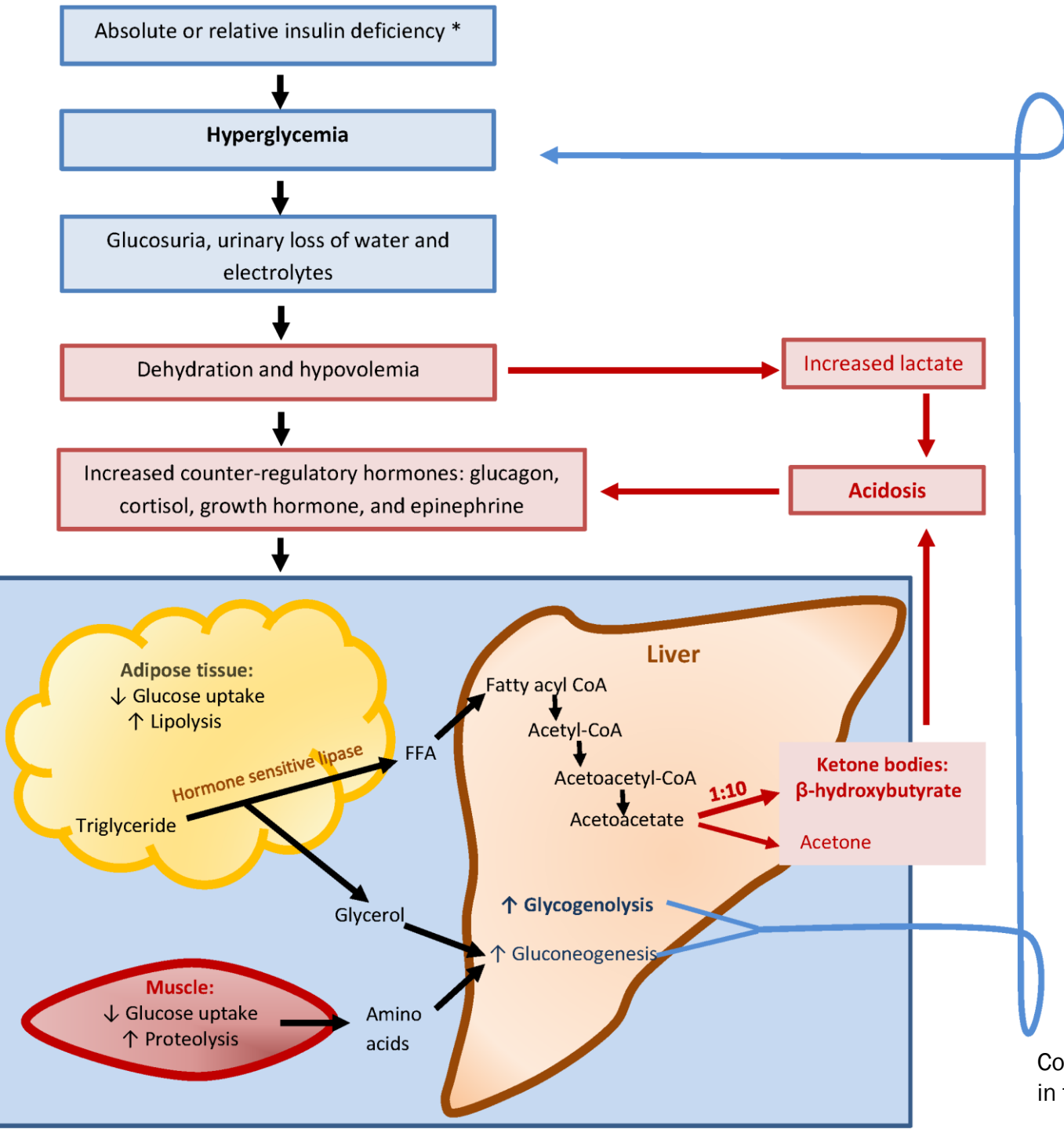
SGLT-2i and Insulin



- Glucose spills into urine at lower plasma concentration
- Decrease in circulating insulin
 - Mild relative hypoinsulinemia
- Increased gluconeogenesis and FFA metabolism
- Increased baseline glucagon
 - Promotes ketogenesis
- Promotes negative fluid and sodium balance

Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Research & Care*. 2023;11:e003666.

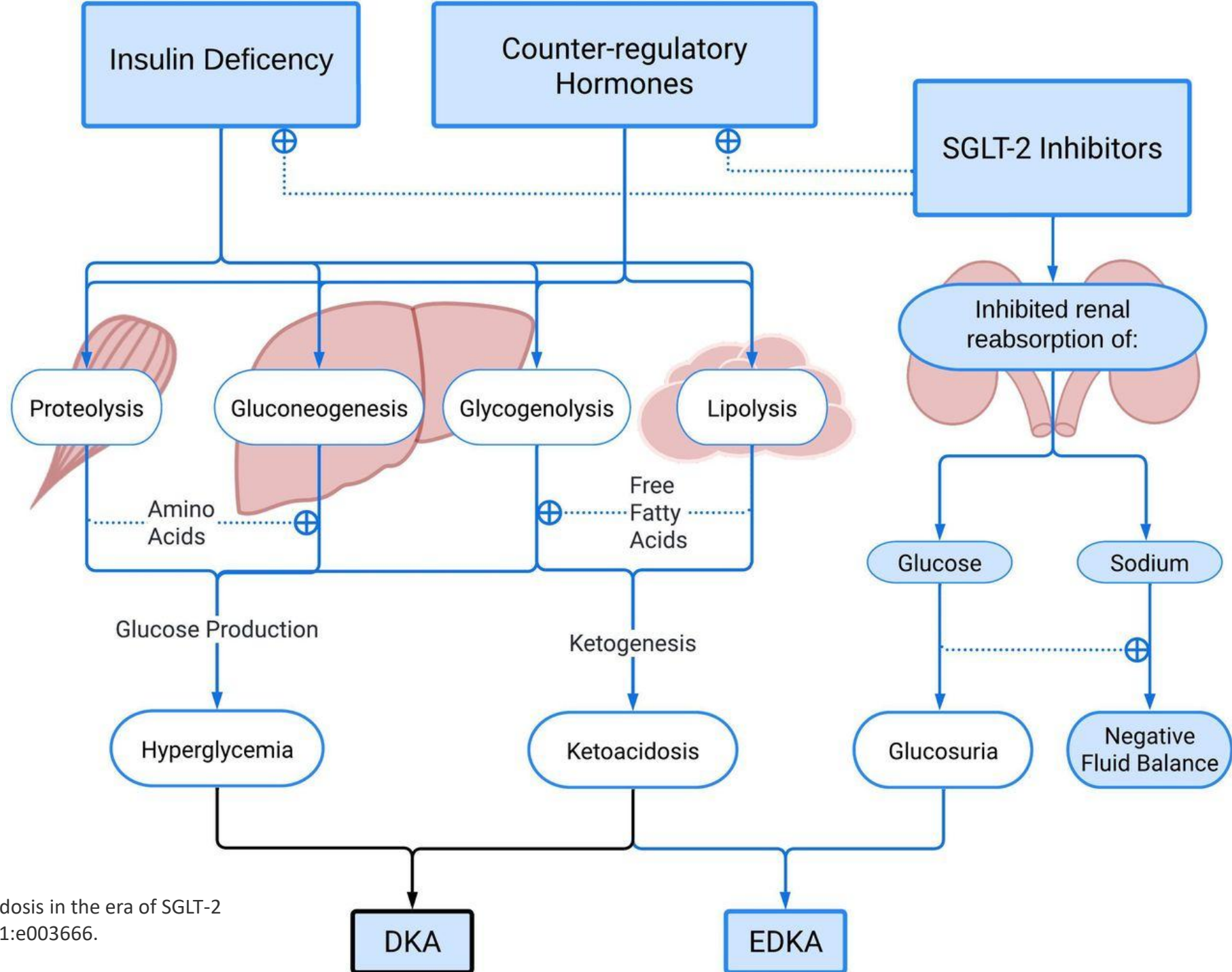
<https://doi.org/10.1136/bmjdr-2023-003666>



DKA Pathophysiology

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Euglycemic DKA



Euglycemic DKA Diagnosis



- **D:** glucose $<200^*$ mg/dL with Hx DM or SGLT-2i
- **K:** Ketosis
 - Beta-hydroxybutyrate level ≥ 3 mmol/L and
- **A:** Metabolic acidosis
 - pH <7.3 or
 - Bicarbonate concentration < 18 mmol/L
 - Elevated Anion Gap

Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Research & Care*. 2023;11:e003666. <https://doi.org/10.1136/bmjdr-2023-003666>

Differential Diagnosis

- Alcoholic ketoacidosis
- Starvation ketosis
 - Milder ketosis
 - Higher bicarb
 - No acidosis
- Lactic Acidosis
- Other HAGMA

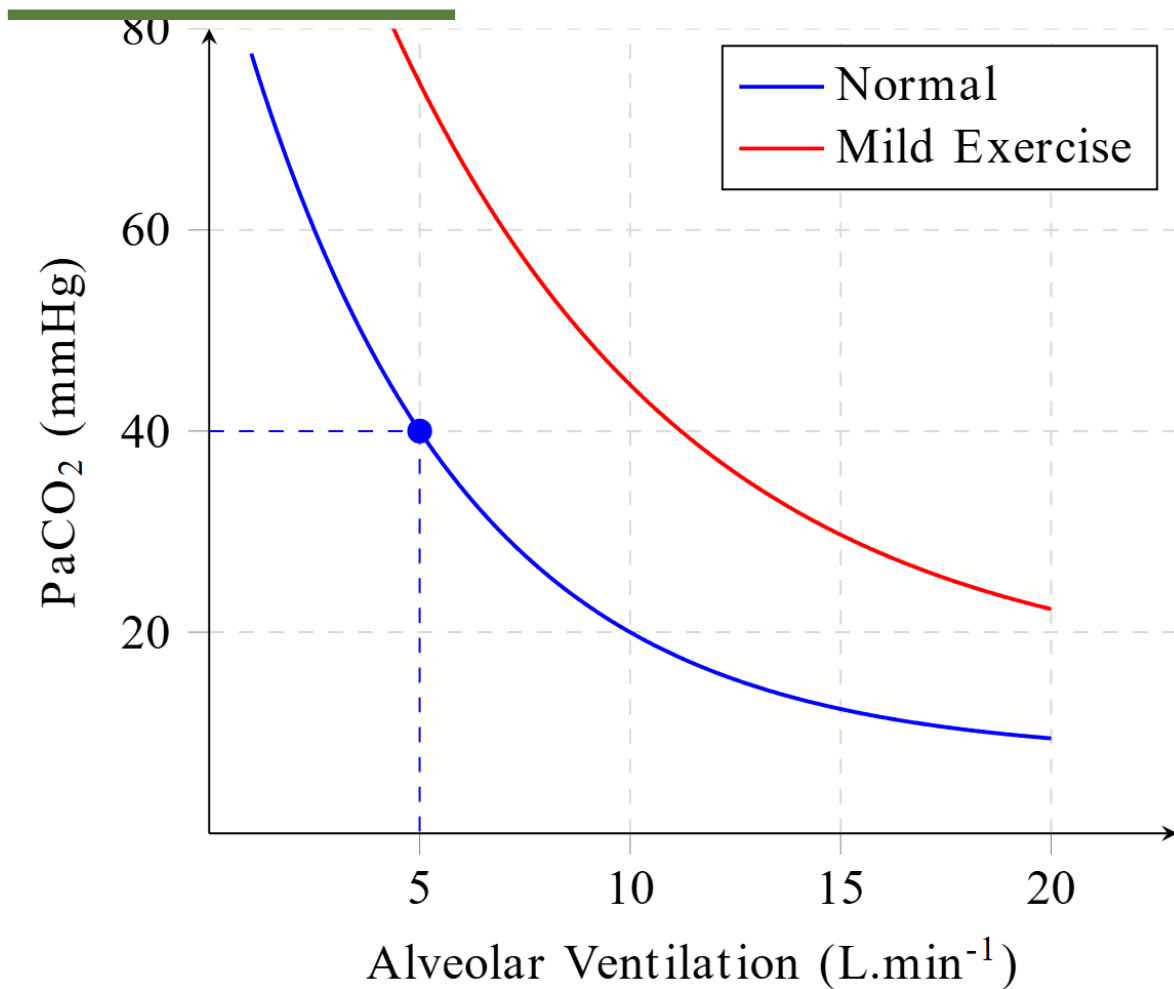


A Word of Caution

- pH isn't everything
- Respirations compensate for metabolic acidosis
- Respiratory compensation in DKA can be profound
- Outstripping of compensation is precipitous



PCO₂ vs Ventilation



A Classic ABG

- pH: 7.18
- pCO₂: 28
- pO₂: 124
- HCO₃: 9



A Likely ABG

- pH: 7.32
- pCO₂: 20
- pO₂: 124
- HCO₃: 7



Another Likely ABG

- pH: 7.32
- pCO₂: 30
- pO₂: 124
- HCO₃:15



Euglycemic DKA Management

- **Prevention**

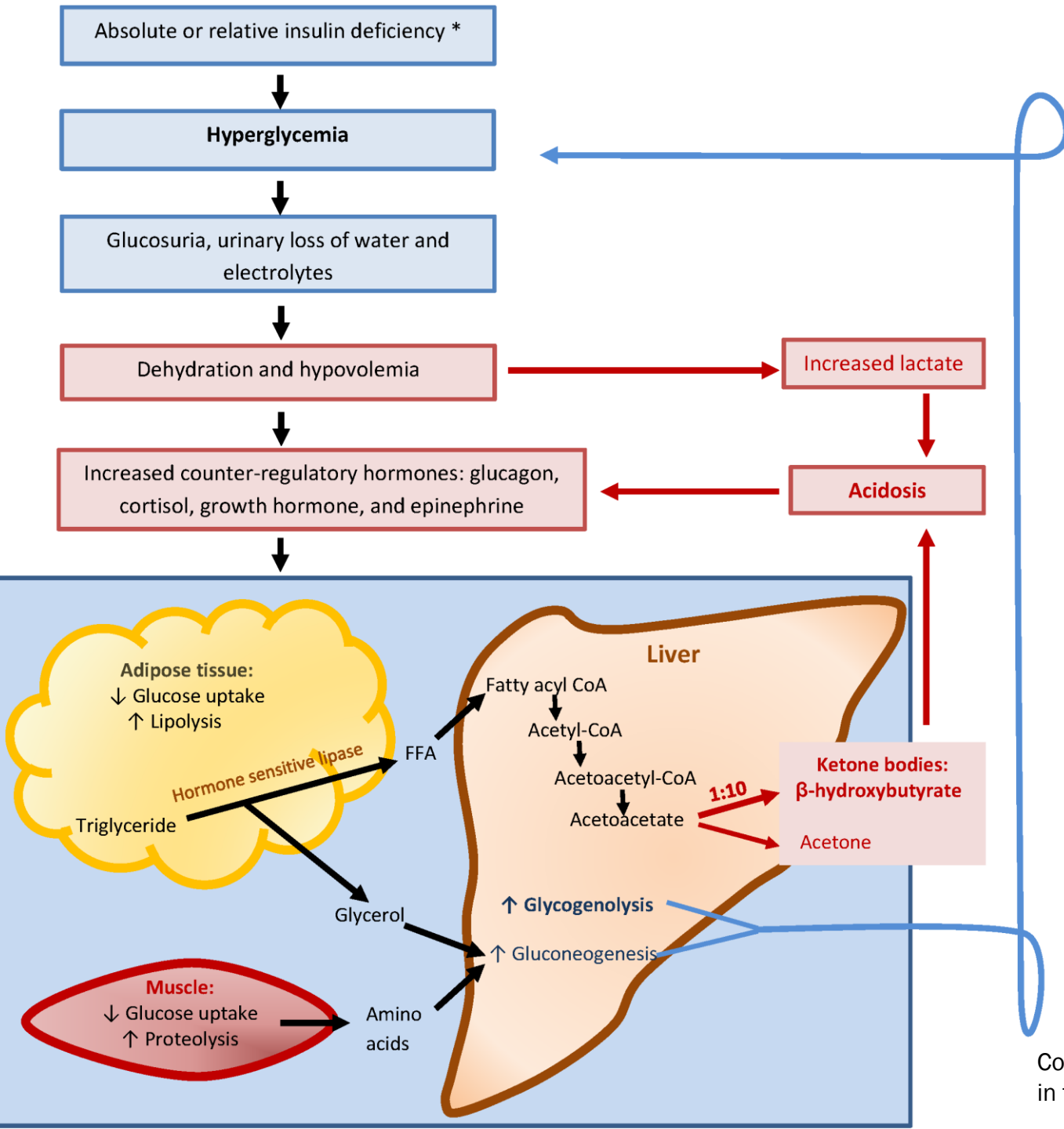
- Hold SGLT-2i 3 days prior to major surgery (esp cardiac)
- Pause SGLT-2i in acute illness
 - Follow urine ketones on outpatient basis
 - Low threshold to check serum ketones in pts with nausea, vomiting, or malaise



Euglycemic DKA Management

- Similar to Regular DKA
 - Fluids
 - Potassium
 - Insulin





DKA Pathophysiology

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Insulin Management

- Determine Severity of DKA
 - How to determine?
 - Serum glucose?
 - pH?
 - Bicarb?
 - Respiratory compensation?



Insulin Management

- Higher risk of relapsing into DKA if on SGLT-2i
 - Our practice: observe in ICU 24hr after gap closure/resolution
 - Patient population specific



Insulin Management



- **Mild-moderate**
 - IV Dextrose
 - IV Insulin infusion 1-3U/hr
 - No initial bolus

- **Moderate-severe**
 - Hospital “DKA Protocol”
 - IV Dextrose
 - IV Insulin infusion 0.1U/kg/hr
 - No initial bolus

Citations



- Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Research & Care*. 2023;11:e003666. <https://doi.org/10.1136/bmjdr-2023-003666>
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