DR N K SINGH
NATIONAL EC MEMBER RSSDI
DHANBAD

- **Director, Diabetes and Heart Research Centre, Dhanbad**
- **Executive Member, National RSSDI(2022-2025)**
  Ex Governing body member, National API, National (2019-2023)
  Ex Chairman API Jharkhand and Chairman RSSDI ,Jharkhand.
- **Edited Millennium Book of Medicine, RSSDI Case File Book 2024,Asso.editor,Postgrduate Medicine2021**
- **Edited Mongraph on COVID by ICP/API 2023**
  Over 45 national and international publications
- **Admin and founder CME INDIA WhatsApp Gr**
  Editor:www.cmeindia.in

eDKA:A critical Must-Know in Modern Diabetes Care

Dr NK Singh
MD,FICP,FACP,FRSSDI

National EC Member RSSDI
Diabetologist Physician, Dhanbad

Director Diabetes & Heart Research Centre,Dhanbad
Editor/Admin : CME INDIA

FIRST DESCRIBED in 1973

- EDKA was first described in 1973 by Munro as a rare occurrence in patients with insulin-dependent diabetes.
- Of the 211 episodes of DKA in this report, 37 could be considered euglycemic with BG levels <300 mg/dL.
- In later years, reports indicated that approximately 2.6%–3.2% cases of DKA presented with euglycemia.
- However, there is evidence of a changing trend from these early reports of EDKA as the use of SGLT-2 inhibitors increases

THE CLINICAL LESSON

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors **Diabetes Care 2015;38:1638–1642** | DOI: 10.2337/dc15-1380

- **20 clinical cases requiring hospitalization captured between March 2013 and June 2014 in the FDA Adverse Event Re-porting System database.**
- **The scarce clinical data provided suggested that most of the DKA cases were reported in patients with type 2 diabetes (T2D), for whom this class of agents is indicated.**

The Problem

- Approximately 2.6% to 3.2% of DKA admissions are euglycemic.
- DKA-associated with the use of SGLT2 inhibitors has rates ranging from 0.16 to 0.76 events per 1000 patient-years in patients with type 2 diabetes.
- Blau et al estimate that the SGLT2 inhibitors increase the risk of DKA in T2D patients by 7-fold.
- Erondu et al estimate an overall incidence of DKA from SGLT2 inhibitor use of approximately 0.1%. Data on patients with type 1 diabetes who presented with DKA associated with SGLT2 inhibitors showed rates varying from 5 to 12%; however, euglycemia was not present in all cases

Which one more dangerous ? DKA or eDKA ?

- **Typical DKA has a mortality rate of 0.65%–3.3%.**
- **Given the diagnostic dilemma of normoglycemia or lower-than-expected BG levels, EDKA portends worse outcomes compared with classic DKA.**
- **Most available data on mortality and morbidity of EDKA relates to the condition occurring in pregnant women. Maternal EDKA can increase the rate of fetal demise (up to 9%) and increases maternal mortality.**

Once upon a time…….

Missing Window

Case by Dr Pratap Jethwani

(RSSDI Case Files)

- Male 52 years old
- Having T2DM since 7 years (diagnosed at the age of 45 years)
- Taking Rx since 2021 from Rotary Diabetes Clinic at Rajkot
- Not having any complaints
- Was taking since June 2021
  - Pioglitazone 15 mg + Metformin SR 500 mg od
  - Dapagliflozin 10 mg + Metformin SR 500-1000 mg od
  - Rosuvastatin 10 mg od

- Family History : Uncle having DM
- Last visit 8 May 23

  Height :166 cms

  Weight : 65 Kg

  BMI : 23.59 kg/mt2

  Pulse : 88/ min

  BP : 128 / 70 mm Hg

  Investigations : HbA1c - 5.6%,

  TC-130 mg%, TG-97 mg% , LDL- 63.20 mg%

  HDL- 47.4 mg%, S. Creatinine : 0.7 mg%, eGFR-110 ml/min

CASE HISTORY - BACKGROUND

DEPARTMENT OF MEDICAL RECORDS
GOVERNMENT S.M.H.S. HOSPITAL, SRINAGAR, KASHMIR.
(An Associate Hospital of Govt. Medical College, Srinagar.

DISCHARGE SUMMARY

₹:10/-

(Patient's Copy)

INVESTIGATIONS:

CBC:
Hb: 12.4/15/12.4
TLC: 11k/25k/11.95k
N: 81%/76%/
L: 8%/3%
PLT: 295/202
MCV: 100/85.7
CH: 30/29

KFT
Glu 235/158/210/152
Urea: 44
Crea: 0.9
Na^+: 140
K^+: 2.8
Bil: 0.6
TP: 6.9
Alb: 4.0
Alkp: 75
AST: 40
ALT: 38

Ca^{2+}: 8.5
PO_4^{2-}: 2.5
Na^+: 138

Urine For Ketones → ⊕

NBG
pH: 7.01/7.3/7.36
HCO_3 = 4.5/11.3/18
PCO_2 = 18/23/35
lac: 1.2/0.8/0.7

OPERATION / MANAGEMENT:

ECG → NSR –

RUTE: Sugar 4+ ketones: 3+
pus cells ?

IN HOSPITAL STAY / POST OPERATIVE STAY:

⊖ Stop OADS
⊖ inj insulin (R) 10 U iv stat 7/b
insulin (R) infusion @ 10 U / hr.
⊖ inj KCl as per required.
⊖ syp potchlor 30 ml NSR TDS.
⊖ inj NS% iv infusion as per need.

ADVICE ON DISCHARGE:

Rx at Discharge.

⊖ inj insulin (R) 12U SC ← BBF: Stop ⊗ Dapagliflozin
BLN
BDN

Adv
Follow up us [illegible]
21 after
2 week on
wednesday

⊖ inj insulin (N) 10 U S/C ~~BD~~ BD
[illegible]
⊖ syp potchlor 30 ml NSR BD x 3 days
⊖ Tab Neurobion Forte 1 tab BD 1 x n gm
⊖ Tab pantop 40 BBF 1 tab x 1 x [illegible]

Sig. of Resident Incharge

- He was diagnosed to have Euglycemic Diabetic Ketoacidosis and was treated with IV insulin infusion, IV fluids & supportive treatment.
- He was discharged on 03/08/2023 on basal -bolus insulin therapy (NPH 10-0-10 & REGULAR 12-12-12) with Potasium Chloride orally, B complex & Pantoprazole

Date of Admission / Time 31/07/23 Date of Discharge/Time 03/08/23

DIAGNOSIS → 53yr/M U/L T2DM on Rx ← Dapa – 10 mg
metformin
Pioglitazone – 15mg

↓

Non-compliant to Rx for 3 days.

CASE SUMMARY:

C/O:
- Vomiting
- Abdominal pain
- Hyperventilation

∴ = Euglycemic keto acidosis

???

Is this euglycemic DKA ?

Is it due to SGLT2 inhibitor ?

What will be the next step ?

Any investigations required at this stage ?

Is this euglycemic DKA ?

Euglycemic diabetic ketoacidosis (DKA, EDKA) is a clinical syndrome occurring both in T1DM & T2DM characterized by

- Euglycemia (blood glucose ≤ 250 mg/dL)
- Metabolic acidosis

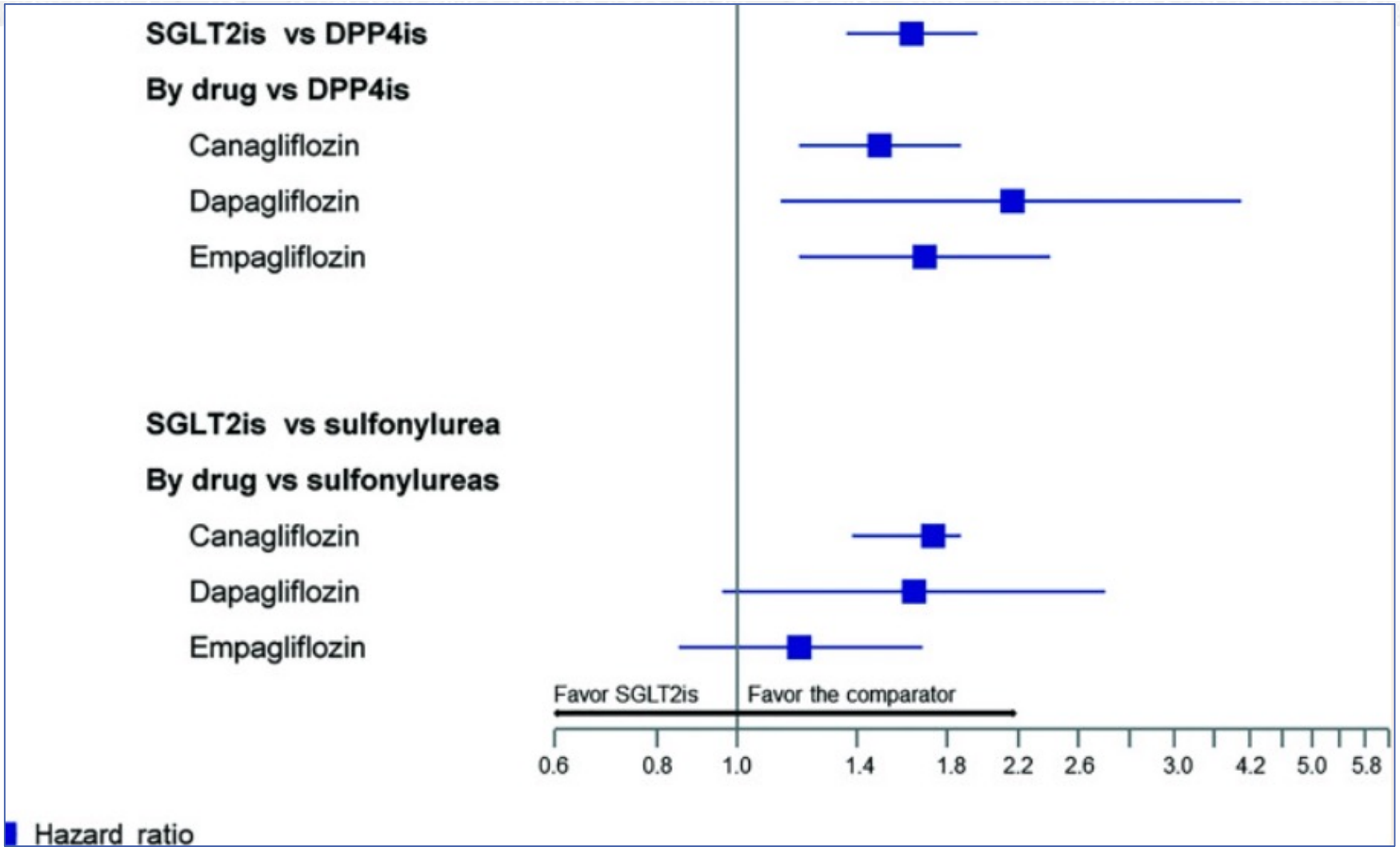
  (arterial pH < 7.3, serum bicarbonate < 18 mEq/L)
- Ketonemia

Why happens ?

Anti-Diabetic Agent	Mechanism of Action	Ketogenic Potential
SGLT-2 Inhibitors	Inhibit glucose reabsorption in the kidney, leading to increased urinary glucose excretion	Promote mild ketogenesis due to increased free fatty acid availability and decreased insulin secretion
Metformin	Decreases hepatic glucose production and improves insulin sensitivity	Low potential → Does not promote ketogenesis
Sulfonylureas	Stimulate insulin secretion from β cells in the pancreas	Low potential → Does not promote ketogenesis
DPP-4 Inhibitors	Inhibit the enzyme DPP-4, which breaks down incretin hormones that stimulate insulin secretion	Low potential → Does not promote ketogenesis
GLP-1 Receptor Agonists	Mimic the action of GLP-1, an incretin hormone that stimulates insulin secretion and decreases glucagon secretion	Low potential → Does not promote ketogenesis
Insulin	Facilitates glucose uptake by cells and decreases hepatic glucose production	Low potential → Does not promote ketogenesis

SGLT2-Inhibitors

Rate of diabetic ketoacidosis with SGLT2 inhibitors compared with DPP-4 inhibitors and sulfonylureas among patients with T2DM



Diabetes Care. 2022;45(4):919-927

Precipitati…cidosis and their

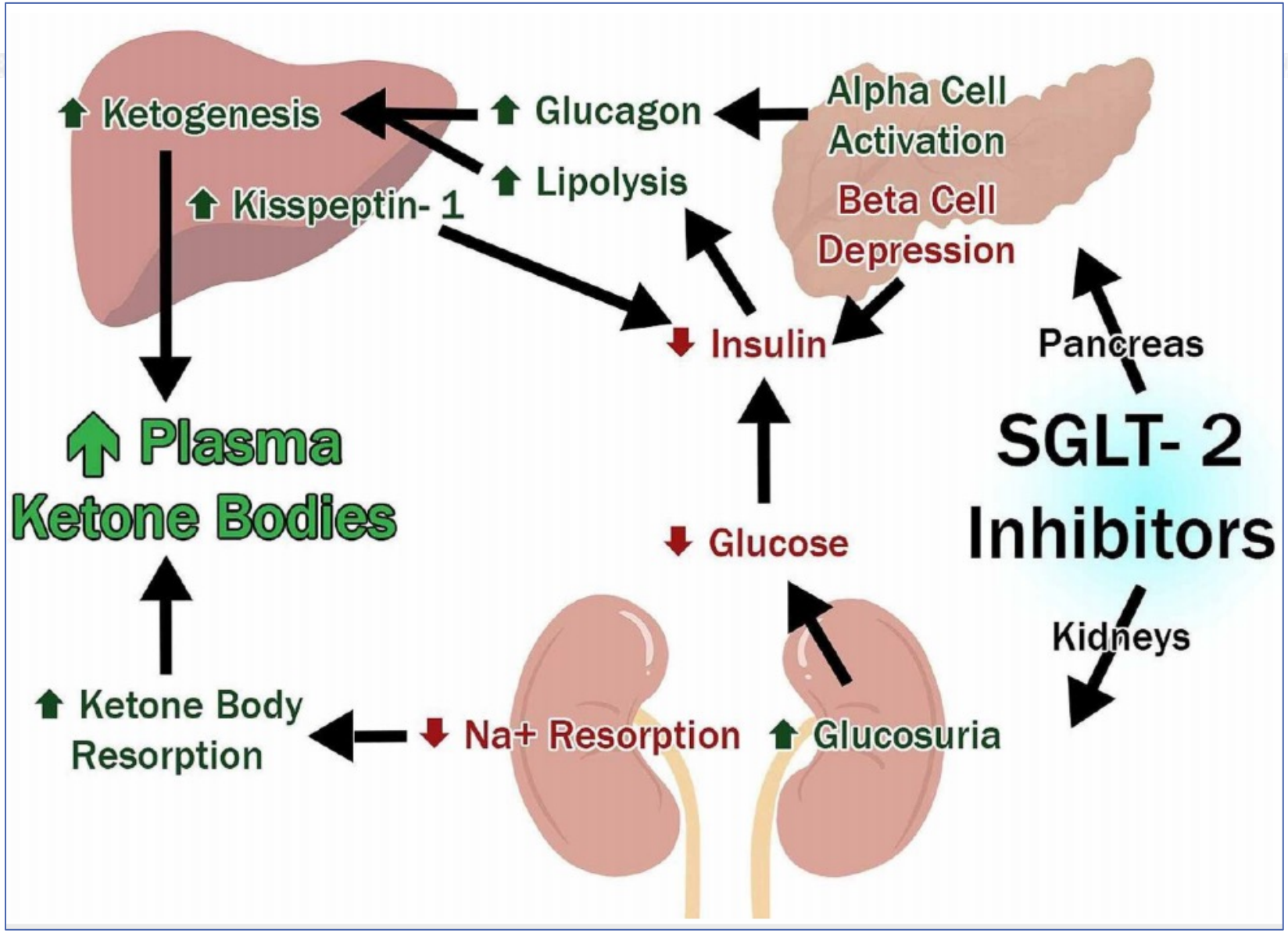
Risk factors	
Infection	…), increased peripheral glucose utilization,
Surgery	…is prolonged and/or gut absorption is slow
Fasting	…M
Alcohol intake	…droxybutyrate) due to altered NADH/NAD
Acute vascular events (ACS or stroke)	
Trauma	…ution by large fluid shifts during
Prolonged physical activity or exercise	…, decreased carbohydrate intake

Conditions associated with euglycemic diabetic ketoacidosis in patients with diabetes

- SGLT-2 inhibitors (especially in patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus with low insulin reserve)
- Anorexia/prolonged hunger
- Pregnancy
- Surgery
- Trauma
- Infections
- Acute coronary syndrome
- Acute cerebrovascular diseases
- Prolonged physical exercises
- Ketogenic diets
- Alcohol consumption
- Cocaine use
- Drugs affecting carbohydrate metabolism (glucocorticoids, high-dose thiazide diuretics, sympathomimetic agents, etc.)
- Hepatic and renal diseases
- Acute abdomen (appendicitis, gastroenteritis, pancreatitis, cholecystitis, etc.)
- Glycogen storage diseases
- Pump failure in patients with insulin pumps
- Interruption or discontinuation of treatment in insulin-dependent patients

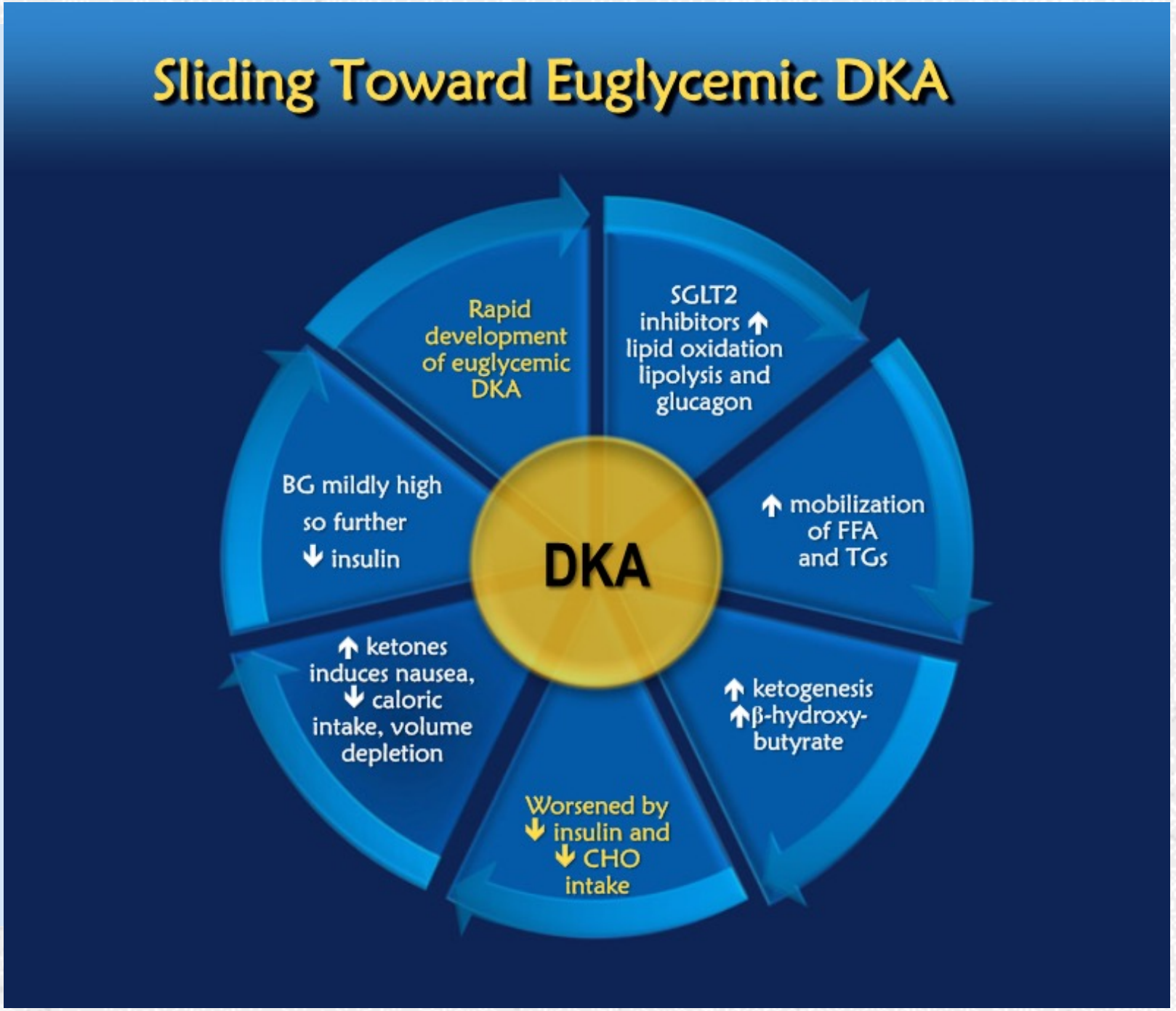
SGLT-2: Sodium–glucose transporter 2

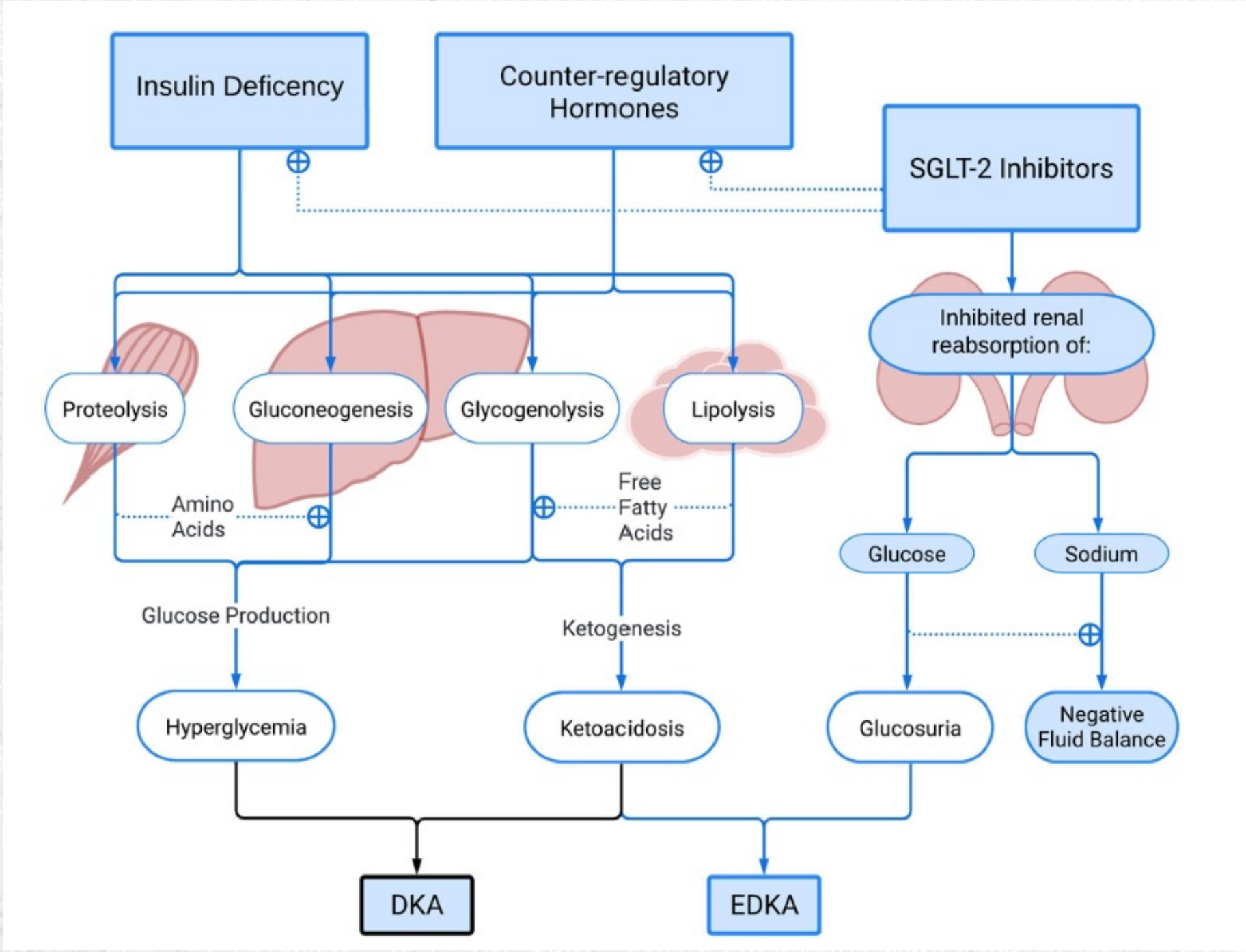
Pathophysiology and mechanism of SGLT2i causing EDKA



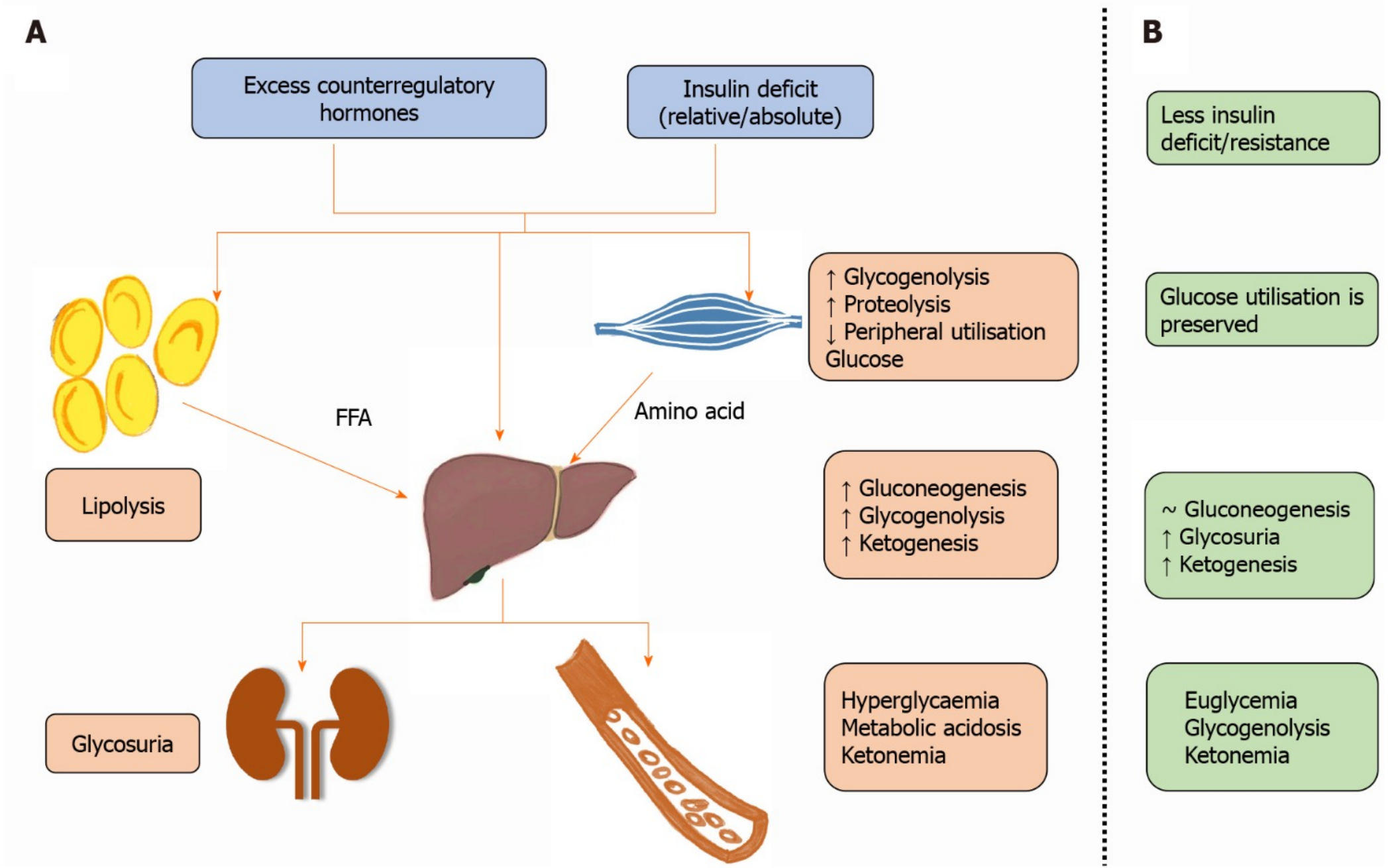
Somagutta M R, et al. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. Cureus 2021; 13(3): e13665.

- Absolute insulin deficiency leads to reduced glucose utilization and enhanced lipolysis
- Increased delivery of free fatty acids(FFAs) to the liver coupled with raised glucagon levels promotes
- FFA oxidation and production of ketone bodies. In both T1D and T2D, DKA presents with marked hyperglycemia (>250 mg/dL,typically 350–800 mg/dL), profuse glycosuria and hyper-ketonemia (plasma b-hydroxybutyrate (4.2–11.0 mmol/L)
- The hyperglycemia of DKA is associated with extreme insulin resistance, manifesting itself as markedly reduced tissue glucose disposal and increased endogenous glucose production (EGP)



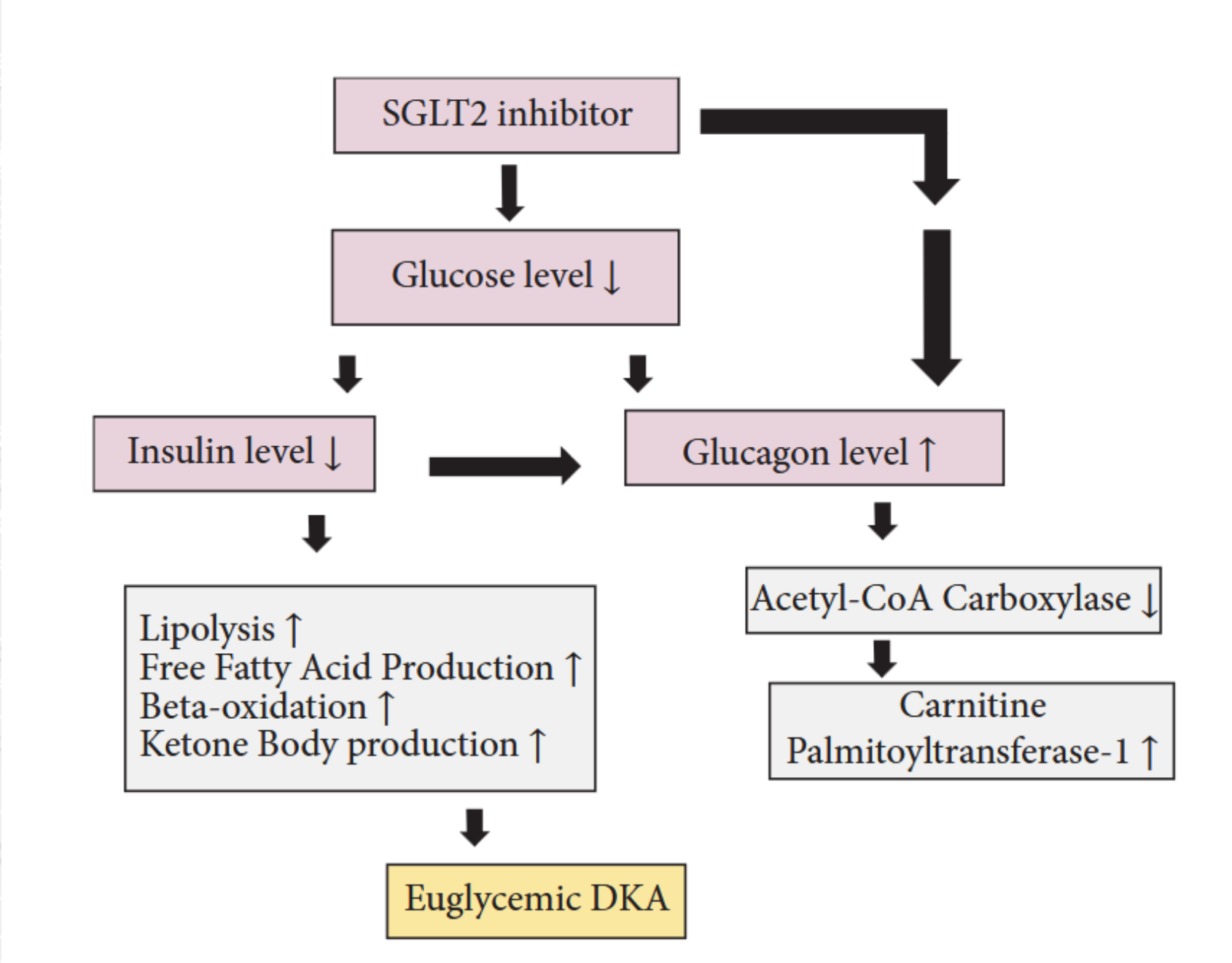


Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. BMJ Open Diab Res Care 2023;11:e003666. doi:10.1136/bmjdrc-2023-003666


A
Excess counterregulatory hormones
Insulin deficit (relative/absolute)
↑ Glycogenolysis
↑ Proteolysis
↓ Peripheral utilisation
Glucose
FFA
Amino acid
Lipolysis
↑ Gluconeogenesis
↑ Glycogenolysis
↑ Ketogenesis
Glycosuria
Hyperglycaemia
Metabolic acidosis
Ketonemia
B
Less insulin deficit/resistance
Glucose utilisation is preserved
~ Gluconeogenesis
↑ Glycosuria
↑ Ketogenesis
Euglycemia
Glycogenolysis
Ketonemia

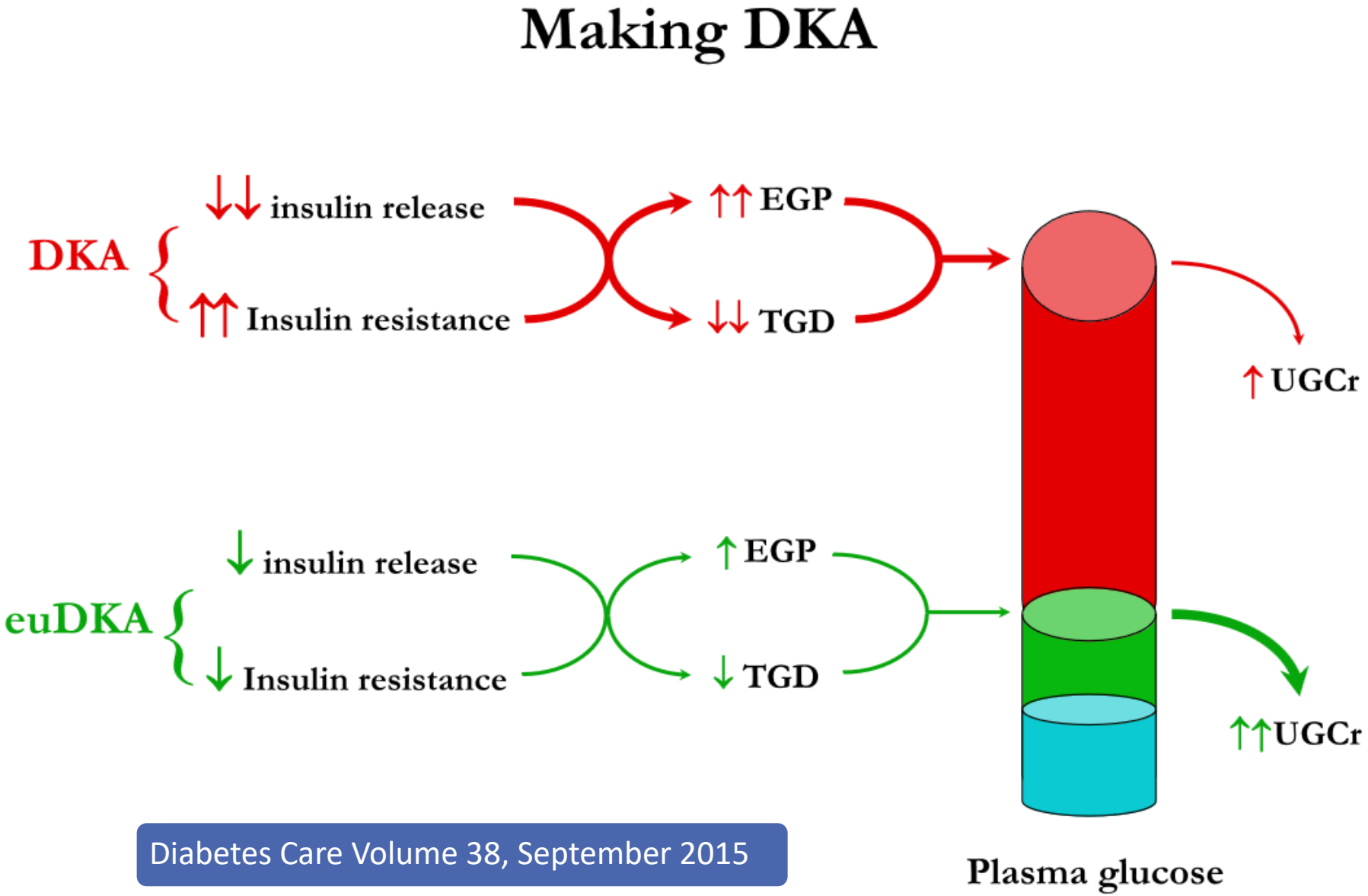
- **Ketoacidosis follows with the same sequence of events in euDKA as in DKA.**

- **In SGLT2-treated T2D patients, the lower insulin-to-glucagon ratio stimulated lipolysis (circulating FFAs are 40% higher during the meal) and enhanced lipid oxidation (by 20% on average) at the expense of carbohydrate oxidation (which fell by 60%)**



Essential pathophysiology of DKA and euDKA consequent of the use of SGLT2 inhibitors.

TGD, tissue glucose disposal;
UGCr, urinary glucose clearance



Diabetes Care Volume 38, September 2015

Overall, euglycemic diabetic ketoacidosis (euDKA) shares a similar pathophysiology with diabetic ketoacidosis (DKA), except for the unique circumstance of SGLT2 inhibitor-induced glycosuria. This mechanism "artificially" lowers plasma glucose levels, thereby increasing the predisposition to ketogenesis.

Diagnose it !

To make a diagnosis of DKA a triad of hyperglycemia above 250 mg/dL, ketonemia, and metabolic acidosis with elevated anion gap is required.

EDKA is like DKA but lacks the classic hyperglycemia component.

In EDKA, blood glucose (BG) is generally <200 mg/dL, although in some reports a cut-off of 300 mg/dL has been used to define EDKA.

Prefer to use a BG threshold of <200 mg/dL, ketonemia (serum β-hydroxybutyrate≥3.0 mmol/L), and at least one of the following criteria to define EDKA:

1. Arterial pH≤7.3
2. Serum bicarbonate ≤18 meq/L
3. Anion gap >10.

Laboratory Values for DKA and EDKA

Measurement	Reference	DKA	EDKA
Blood glucose[a]	80-130 mg/dL	>250 mg/dL	<250 mg/dL
Arterial pH	7.35-7.45	<7.3	<7.3
Serum bicarbonate	22-26 mEq/L	<18 mEq/L	<18 mEq/L
Urine ketones	None present	Present	Present
Serum ketones	None present	Present	Present
Anion gap	0 mEq/L	10-12 mEq/L	10-12 mEq/L

[a] Nonfasting. DKA: diabetic ketoacidosis; EDKA: euglycemic DKA. Source: References 1, 7-9.

EDKA can be further classified as

- **Mild with a pH range of 7.25–7.3 and/or serum bicarbonate 15–18 meq/L,**
- **Moderate with a pH 7.00–7.24 and/or serum bicarbonate 10–15 meq/L, or**
- **Severe with a pH<7.0 and/or serum bicarbonate <10 meq/L.**

Stages of EDKA caused by exposure to SGLT-2 inhibitor

Stage 0	Stage 1	Stage 2	Stage 3
Ketones negative AG<15 Glycosuria	Ketones in low quantity or negative AG<15 Glycosuria	Ketones in moderate or large quantity AG<15 Glycosuria	Ketones in moderate or large quantity AG>15 Glycosuria

AG, anion gap; EDKA, euglycemic diabetic ketoacidosis; SGLT-2, sodium-glucose transporter type 2.

Physicians and patients need to be made aware that such risk may be increased in long-standing T2D patients with marked b-cell insufficiency or in latent autoimmune diabetes in adults with rapid evolution toward T1D and during prolonged starvation, after surgery, or during intercurrent illness.

In T1D, however, the euDKA risk appears to be more concrete for reasons entirely within the pathophysiology:

1) in T1D patients hyperglycemia typically is higher than in T2D patients,
2) in early T1D glomerular filtration rate may be increased,
3) insulin may en- hance the effect of SGLT2 inhibition on glycosuria, and
4) changes in insulin dose are not infrequent and may be inappropriate for the amount and kind of carbohydrate intake.

Must Know this

First, inappropriate reductions of insulin doses or any factor that may increase insulin demand, such as stress, a sick day, or even alcohol intake, may induce hyperketonemia.

Under these circumstances, initially patients may just not feel well or experience some malaise and perhaps -Mild nausea with no vomiting.

Their first impulse is to check their blood glucose; because of the persistent glycosuria, glycemia will be only mildly elevated so that they would tend to reduce or with-hold insulin and avoid eating.

These maneuvers will accelerate ketone production and metabolic decompensation toward DKA. The metabolic picture will be further compounded by the volume depletion caused by the persistent glycosuria and vomiting.

How difficult to recognize

euDKA is in fact easily detectable because reliable tools are currently available to

sh ny

This should be part of any educational element for those treated with an SGLT2 inhibitor

time an SGLT2 inhibitor–treated patient feels unwell regardless of the ambient glucose levels.

History and Physical

- Signs and symptoms vary on a case-by-case basis but are similar in presentation to hyperglycemic DKA, although perhaps without polyuria, polydipsia, or severe mental status changes.

- EDKA patients can present with nausea, vomiting, shortness of breath, generalized malaise, lethargy, loss of appetite, fatigue, or abdominal pain. Patients may not have polydipsia or polyuria since serum glucose is normal.

- The onset can be more insidious compared to hyperglycemic DKA due to the mechanism of subacute starvation required to induce ketosis and dehydration. There may or may not be an inciting infection or stressors, such as pregnancy, surgery, pancreatitis, alcohol use, or fasting.

History and Physical

- Patients may present with deep, rapid breathing, known as Kussmaul respiration, which represents respiratory compensation for severe metabolic acidosis.

- They may have a fruity odor to their breath due to the loss of acetone.

- Tachycardia, hypotension, altered mentation, increased skin turgor, and delayed capillary refill are all signs of total body fluid loss. In severe cases, severe dehydration and metabolic derangement can lead to hypovolemic shock, lethargy, respiratory failure, coma, and death.

Diagnosis

- **A thorough history must be obtained, and assessment of medications is essential, including off-label and surreptitious use.**
- **History should elicit ingestion of substances that may predispose to metabolic acidosis, such as alcohol.**
- **Presentations of alcohol-associated ketoacidosis (AKA) may have significant overlap with DKA and EDKA.**
- **Assessment of serum ketones may be revealing, as AKA exhibits a higher ratio of beta-hydroxybutyrate to acetoacetate as compared with DKA (19:1 AKA vs 11:1 DKA).**

- **A metabolic panel and serum ketones should be obtained early in the presentation to evaluate for acidosis and ketonemia.**
- **Anion gap acidosis in the absence of elevated ketones should prompt further investigation for other causes including sepsis, lactic acidosis, renal failure, ingestion of alcohol, methanol, or polyethylene glycol, and overdose with salicylates and tricyclic acids.**
- **As EDKA is a diagnosis of exclusion, other causes of acute anion gap acidosis must be excluded**

Evaluation

- An ill-feeling patient with diabetes with symptoms such as malaise, dyspnea, nausea, or vomiting should undergo screening with serum pH and blood or urine ketone testing.
- The initial laboratory evaluation of EDKA includes basic electrolytes, glucose, calcium, magnesium, creatinine, BUN, serum and urine ketones, beta-hydroxybutyric acid, arterial or venous blood gas analysis, lactic acid, chest radiograph, and electrocardiogram. Urine screening for ketones with nitroprusside reagent does not measure beta-hydroxybutyrate but detects acetone and acetoacetate.
- Serum levels of beta-hydroxybutyrate are typically greater than 3 mmol/L in EDKA (normal values less than 0.5 mmol/L). Consider CBC with differential white blood cell count and blood cultures if an infection is on the differential.
- Serum osmolality, to assess for an osmolar gap and toxic alcohols, should be sent to rule out toxic alcohol ingestion when suspected in any patient with severe, unexplained anion gap metabolic acidosis.
- Close attention should be paid to the anion gap to help narrow direct diagnosis, workup, and management.

- The patient has normoglycemia (capillary blood glucose less than 250 mg/dL) in the presence of metabolic acidosis (pH less than 7.3) and a total decreased serum bicarbonate (less than 18 mEq/L).

- Serum and urine ketones must be elevated to make the diagnosis of EDKA. Lactic acid may be elevated but should not account entirely for the elevation in the anion gap.

- Leukocytosis may be present in the case of a concurrent infection; however, it is nonspecific and could also be due to hemoconcentration or stress, among other causes.

- Potassium levels vary, but great attention should be paid to the level before starting therapy, as total body potassium is usually depleted.

- Hypomagnesemia and hypophosphatemia can be seen in starvation due to decreased total intake and increased losses.

- Mild hyponatremia may also be seen but is generally less severe than the “pseudo-hyponatremia” seen in profound hyperglycemic states.

Major differences between DKA, euglycemic DKA, starvation ketoacidosis and alcoholic ketoacidosis

J Med Assoc Thai 2020;103(2):183-90

Features	Diabetic ketoacidosis (DKA)	Euglycemic DKA	Starvation ketoacidosis	Alcoholic ketoacidosis (AKA)
Pathophysiology	Imbalance of insulin and counter-regulatory hormones in diabetics	Imbalance of insulin and counter-regulatory hormones combining with carbohydrate deficit in diabetics	Carbohydrate deficit and increase gluconeogenesis	Increase ketogenesis and relative hypoglycemia
Precipitating factors	Intercurrent illness, insulin deficiency	Intercurrent illness, SGLT-2i, pregnancy, glycogen storage diseases, diet restriction	Prolonged fasting	Chronic alcoholism
Plasma glucose	High	Normal-mild elevated (<200 mg/dL)	Low-normal	Low-normal
Degree of acidosis	Variable (mild-severe)	Variable (mild-severe)	Mild	Variable (mild-severe)
Serum HCO_3	Usually <15 mEq/L	Usually <15 mEq/L	Usually >18 mEq/L	Usually <15 mEq/L

Management of DKA - Special Considerations

- Insulin should be delivered at a fixed rate of intravenous infusion until the anion gap corrects and the patient can transition to oral intake. For patients with insulin resistance (ie, body mass index >35kg/m2), insulin infusion at a fixed rate of 2–3 units/hour is often necessary to correct the acidosis.
- Dextrose infusion, preferably 10% dextrose water (D10W) is typically necessary in EDKA to prevent hypoglycemia
- Patients may need longer treatment for DKA in the setting of SGLT-inhibitor use. The chances of relapsing back into DKA are high if the insulin drip is stopped prematurely or the dose of basal insulin is inadequate. Therefore, the patient should be closely monitored for an additional 24 hours after the DKA has resolved.

Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. BMJ Open Diab Res Care 2023;11:e003666.

Management

- Initial management should be directed toward fluid resuscitation, as patients usually present as profoundly dehydrated. Begin with the administration of isotonic saline or lactated Ringer solution.

- RSSDI recommends 1 to 1.5 L/hr isotonic fluids during the first 1 to 2 hours. Continuous insulin infusion should follow fluid replacement, contingent on serum potassium levels greater than 3.3 mEq/L, starting at a rate of 0.05 to 0.1 U/kg/hr. In contrast to DKA management, since serum glucose in EDKA is less than 250 mg/dL, dextrose 5% should initially be added to the fluids to avoid hypoglycemia and hasten clearance of ketosis. Consider increasing the amount of dextrose to 10% if ketoacidosis persists on D5%.

- Potassium should also be carefully monitored as total body potassium levels are likely to be depleted, and IV supplementation of potassium and other electrolytes may be needed.

- **Blood glucose levels should be checked hourly, and electrolytes should be checked every 4 hours at a minimum, as is the standard for treating DKA.**

- **Sodium bicarbonate infusions are not indicated and even use in severe acidemia of pH less than 6.9 is controversial.**

- **Patients generally require ICU admission for close hemodynamic and laboratory monitoring and frequent titration of insulin infusion.**

- **Treatment with IV fluid resuscitation should continue until the anion gap closes and acidosis has resolved.**

Differential Diagnosis

- In patients presenting with anion gap metabolic acidosis, clinicians must consider a variety of possibilities early on. Infections, including pneumonia, genitourinary infection, and bacteremia, must be ruled out early in the diagnostic algorithm.

- In patients presenting with abdominal pain, consider intraabdominal infection and pancreatitis. Consider toxic alcohol (methanol, ethylene glycol) or paraldehyde ingestion, salicylate overdose, lactic acidosis, starvation ketosis, and pregnancy in the appropriate clinical setting.

- Patients may have also recently administered insulin, contributing to the euglycemic presentation.

- The presentation is very similar to alcoholic ketoacidosis, except EDKA patients have diabetes, and alcoholic ketoacidosis patients present after an alcohol binge more commonly have hypoglycemia and can be successfully resuscitated with crystalloid and dextrose without the requirement for insulin.

Prognosis

- Most patients with EDKA recover well with prompt recognition and treatment.
- Delayed diagnosis and inadequate treatment, especially hydration without dextrose/insulin infusion, can lead to persistent acidosis, vomiting, and prolonged hospitalization.
- The prognosis is worse for small children and pregnant women.
- Rarely, severe cases of respiratory failure, hypovolemic shock, coma, and death.
- Death is rare in most EDKA cases; however, pregnant women are at greater mortality risk than the general population.

Complications

- Euglycemic DKA can result in persistent vomiting, dehydration, hypoglycemia, hypovolemic shock, respiratory failure, cerebral edema, coma, seizures, infection, thrombosis, myocardial infarction, and death.
- Maternal EDKA can increase the rate of fetal (up to 9%) and maternal mortality.

JAMA Network Open

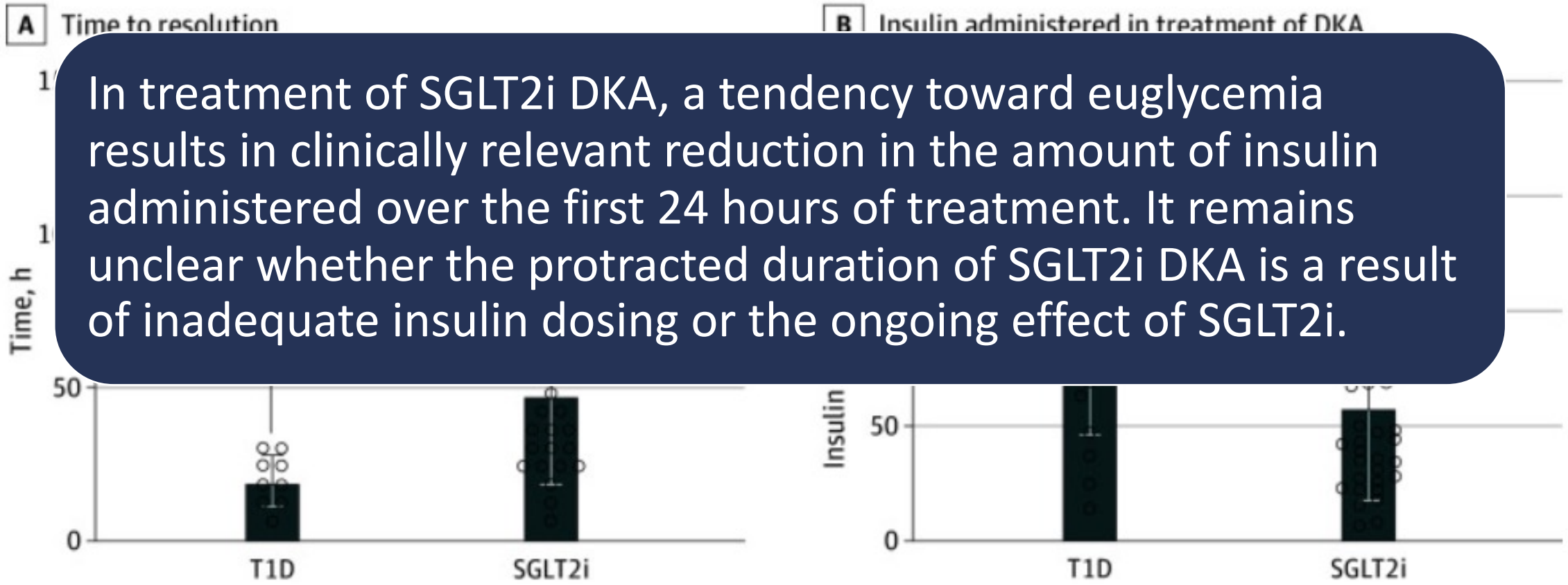
View Article

JAMA Netw Open. 2024 Mar; 7(3): e242744.
Published online 2024 Mar 18. doi: 10.1001/jamanetworkopen.2024.2744: 10.1001/jamanetworkopen.2024.2744

PMCID: PMC10949093
PMID: 38497966

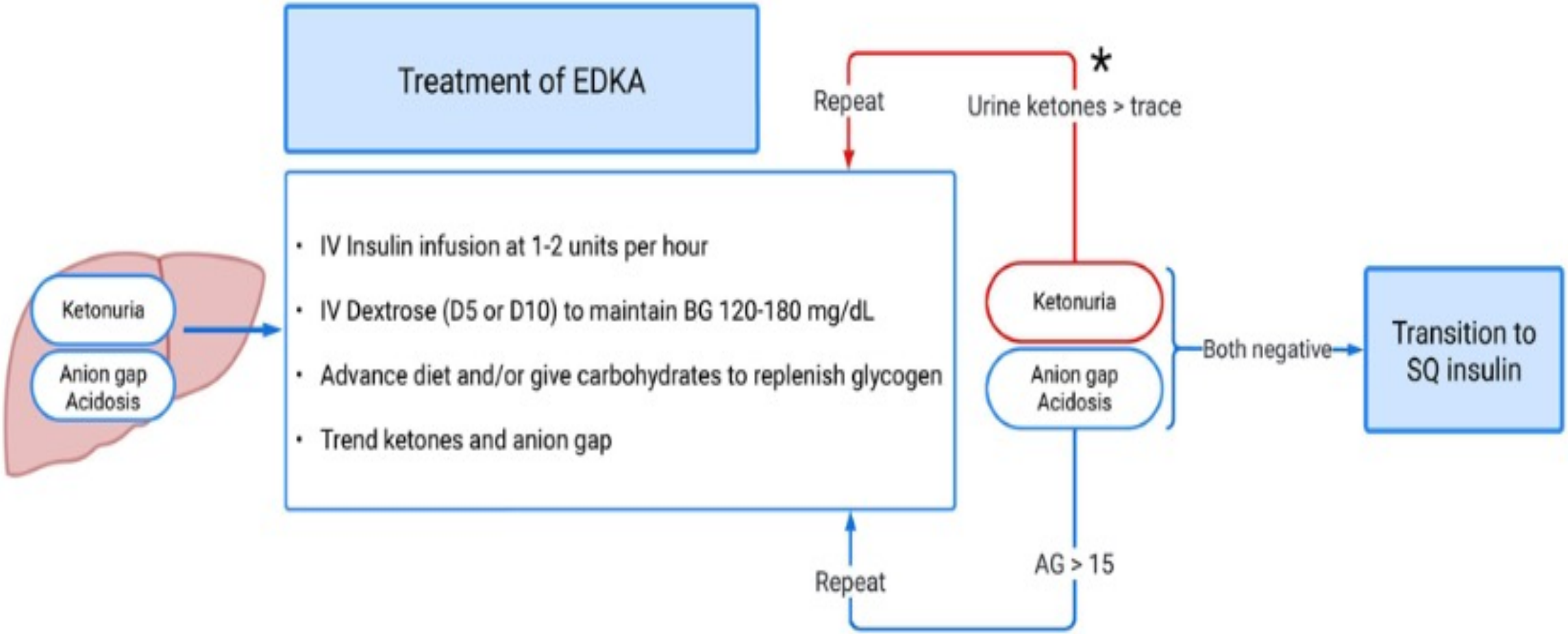
SGLT2 Inhibitor–Associated Ketoacidosis vs Type 1 Diabetes–Associated Ketoacidosis

Mahesh M. Umapathysivam, DPhil,[1,2,3,4,5] Bethany Morgan, MBBS,[2,3] Joshua M. Inglis, MBBS,[2,4] Emily Meyer, PhD,[2,3,4] Danny Liew, PhD,[4] Venkatesan Thiruvenkatarajan, MD,[6] and David Jesudason, PhD[2,3,4,7]



In treatment of SGLT2i DKA, a tendency toward euglycemia results in clinically relevant reduction in the amount of insulin administered over the first 24 hours of treatment. It remains unclear whether the protracted duration of SGLT2i DKA is a result of inadequate insulin dosing or the ongoing effect of SGLT2i.

Manage Simply



Can we restart SGLT2i ?
If Yes, When ?

Can We Restart SGLT2 inhibitors ?

- Restarting a patient's SGLT-2 inhibitor in the immediate period following EDKA was associated with recurrent DKA or symptomatic ketosis.
- Restarting the medication after the resolution of EDKA should be a personalized, share the decision with the patient and physician to determine underlying triggers that may have contributed, mitigate these as appropriate, and address the possibility of recurrence.
- When can we start SGLT2 inhibitor in such patients after an episode of DKA is still not supported by any evidence or expert recommendations

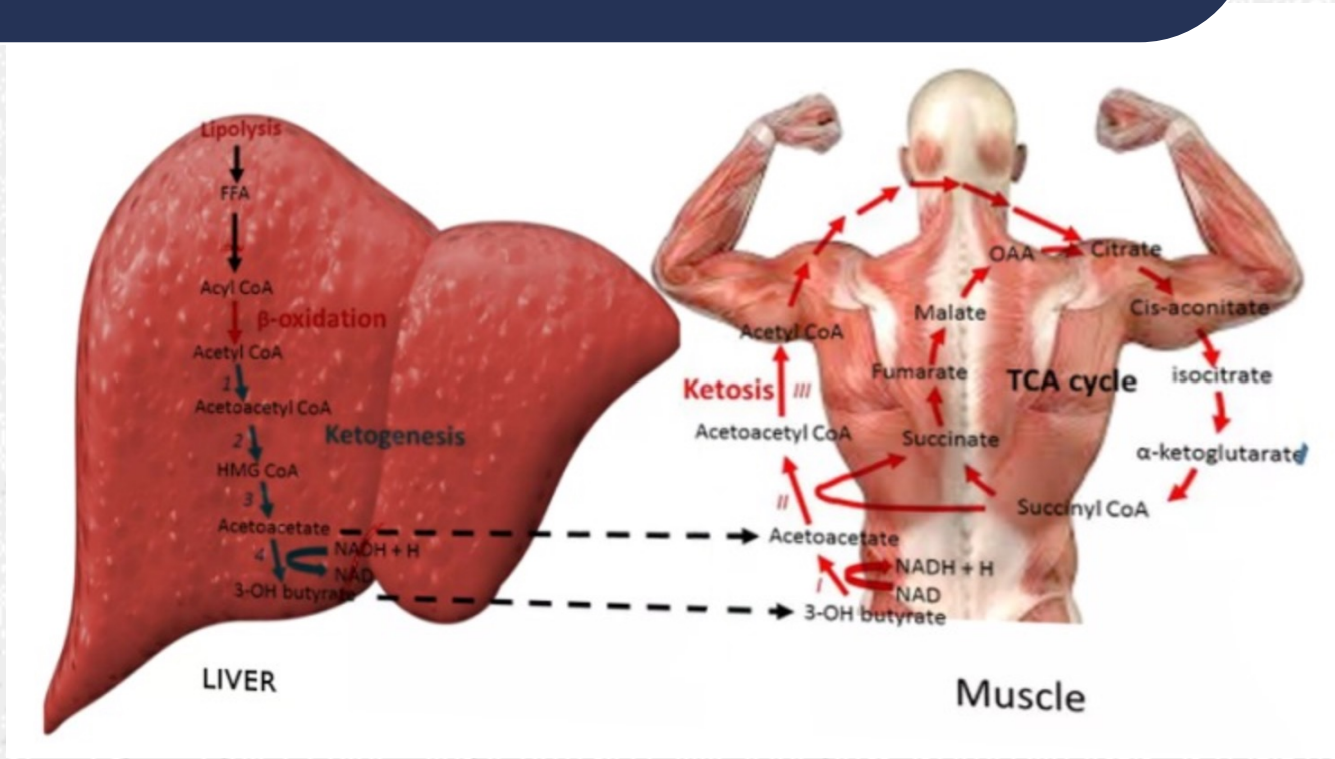
At this time, clinicians should consider pausing SGLT-2 inhibitor 3–4 days before surgery, and insulin therapy should be personalized and adjusted accordingly.

Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. BMJ Open Diab Res Care 2023;11:e003666.

Patients taking SGLT2 inhibitors are at increased risk for diabetic ketoacidosis (DKA). Clinicians often miss the diagnosis of DKA when blood glucose levels are near normal.

Patients with euglycemic DKA are more likely to develop hypoglycemia after initiation of insulin infusion therapy.

Clinical Pearls



If detectable, then euDKA is preventable because detection of significant ketonuria and/or ketonemia any time symptoms such as nausea and/or vomiting or even just malaise disappear, especially after alcohol intake or a recent cut in insulin dose, can prompt advice to maintain vigorous fluid intake and to consume carbohydrates to allow at least full-dose insulin therapy until the ketosis resolves.

Patients should temporarily stop the SGLT2 inhibitor, contact their medical provider, and take supplemental boluses of rapid insulin along with liquids and carbohydrates.

Even if patients are unable to adjust the insulin dose, euDKA can be mitigable by drinking and eating as tolerated without fear of hyperglycemia and seeking prompt medical attention for parenteral fluid replacement and insulin therapy.

Pearls

- Successful diagnosis depends on early screening with serum or urine ketones, even when serum glucose is normal, whenever EDKA is suspected.

- After volume expansion with crystalloid, the foundation of therapy is a combination of dextrose (5 to 10%) and insulin (0.05 to 0.1 u/kg/hr) infusion until acidosis resolves.

- Insulin infusion should not be avoided due to normal glucose levels, but it is essential to successful treatment.

- Ketosis does not resolve with intravenous crystalloid hydration alone.

- SGLT2 inhibitor treatment should be discontinued as soon as EDKA is diagnosed.
- Sodium bicarbonate infusion is not indicated

Must do.....

- **Start insulin with at least 0.05 units/kg/hour along with IV dextrose**

- **Start IV dextrose at 5-10 g/hr . This will be 100-200 mL/hr of a 5% dextrose solution** (dextrose should be added to either normal or ½ normal saline to avoid causing hyponatremia!)

- Dextrose concentrations: D5 = 50 g/L || D10 = 100 g/L || D20 = 200 g/L

- **Euglycemic DKA may present WITHOUT ketonuria if the patient is on an SGLT-2 inhibitor – send a beta hydroxybutyrate!**

- eDKA is most common in the first two months of SGLT-2 inhibitor use, but can happen at any time

Pitfalls

- Not giving enough insulin to reverse ketosis due to concern about low blood sugars
- Not giving enough dextrose to support sufficient insulin dosing
- Not uptitrating insulin for refractory acidosis caused by eDKA

Test Yourself Now

KnowYourself

- A 56-year-old woman presents shortness of breath. A history of present illness reveals nausea but no vomiting, chest pain, or abdominal pain.
- Her medical history includes hypertension, hyperlipidemia, type 2 diabetes, and COPD.
- Vital signs are heart rate 120 bpm, respiratory rate 28 breaths/min, blood pressure 120/70 mm Hg, temperature 37.2 °C (98.9 °F), and Sp02 99% on room air.
- Physical examination shows a distressed woman with deep, prolonged respirations. The findings of the heart, lung, and abdominal examinations are unremarkable.
- An arterial blood gas reveals pH 7.1, pCO2 13 mm Hg, pO2 90 mm Hg, and HCO3 < 6 mEq/L. Chemistry results are sodium 130 mEq/L, potassium 4.0 mEq/L, chloride 100 mEq/L, creatinine 1.3 mg/dL, BUN 24 mg/dL, and glucose 200 mg/dL.
- Urinalysis shows 3+ ketones. Which medication most contributed to the progression and non-recognition of her acute problem?

A.Metformin
B.Glilimipiride
C.Insulin
D.Dapagliflozin

Answer -D

- **Dapa is an SGLT-2 inhibitor associated with DKA with normal or only mildly elevated glucose levels.**

- **SGLT-2 inhibitors affect the proximal convoluted tubule of the nephron to prevent glucose reabsorption. This can lower blood glucose levels without affecting insulin secretion.**

- **Patients with type 2 diabetes can become insulin-deficient enough to develop ketoacidosis without displaying the degree of hyperglycemia that many patients, nurses, and doctors rely on to detect it. In other words, SGLT-2 inhibitors can reduce the hyperglycemia of insulin deficiency without preventing the ketosis of worsening insulin deficiency.**

- **Metformin can cause severe lactic acidosis; however, this patient is in DKA, which is not precipitated by metformin. Glyburide can cause hypoglycemia but is unlikely to result in severe acidosis. Insulin can result in hypoglycemia but is unlikely to cause severe acidosis.**

- A 34-year-old woman with type 2 diabetes mellitus presents to the hospital with malaise and vomiting for three days.
- She is 24 weeks pregnant and has been using less insulin over the last 3 days because of decreased oral intake and normal serum glucose values.
- She also reports an abnormal fruity odor in her urine.
- Laboratory studies show a serum pH of 7.00, bicarbonate of 9 mEq/L, beta-hydroxybutyrate of 7 mmol/L, potassium of 5.1 mEq/L, anion gap of 28 mmol/L, and glucose of 130 mg/dL.

What might have prevented the development of this condition?

A. Early ondansetron use before vomiting became severe

B. Ketone measurement during symptoms of nausea or illness

C. Use of an insulin pump

D. Use of a glucose sensor

Patient education

Patient education

Patient education

Prevention of EDKA in patients taking SGLT-2 inhibitors involves patient education about the mechanisms and symptoms of DKA and EDKA, and a thorough review of the risk factors that can predispose to these dangerous conditions.

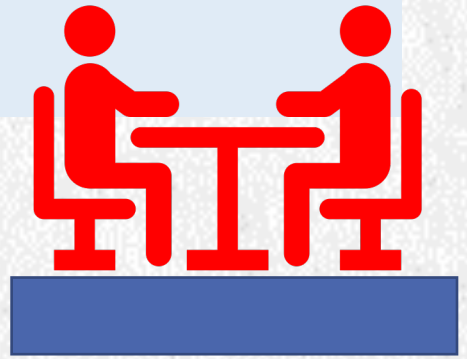
This should also include a discussion on the use of 'sick day rules'. Patients on SGLT-2 inhibitors should be informed that if they start feeling unwell, including nausea and/or vomiting, they should check their BG and consider using a urinary glucose and ketone strip.

Patients should be educated that a normal finger-stick glucose test or continuous glucose monitor readings at home do not preclude the possibility of EDKA.

Further evaluation by a medical provider should not be dissuaded by the absence of hyperglycemia on a home BG test. Fluids and carbohydrates should be consumed along with supplemental boluses of rapid-acting insulin in the time between symptoms and presentation for a medical evaluation

Take Home Points

Euglycemic diabetic ketoacidosis: a potential pitfall for the emergency physician



- **euDKA was originally defined as DKA with plasma glucose levels ,300 mg/dL occurring in young T1D patients, twothirds of whom were female .**
- **The primary cause was reduced availability of carbohydrate, possibly in conjunction with reduced insulin dose.**

Depending on body size, glomerular filtration rate, and degree of hyperglycemia, SGLT2-induced glucose loss can make up a substantial fraction of daily carbohydrate availability.

- **The euDKA reported in T2D patients with SGLT2 inhibitor treatment has a different origin.**
- **Full-dose SGLT2 inhibition induces a rapid increase in urinary glucose excretion, ranging 50–100 g/day equally in men and women and lasting slightly longer than 24 h**
- **In a typical 60-year-old, overweight T2D patient (BMI 28 kg/m2)consuming 50% of daily calories as carbohydrate , this glucose loss amounts to 17–34% of estimated carbohydrate intake in men and 22–44% in women.**

More importantly, renal glucose clearance (i.e., the ratio of glycosuria to prevailing glycemia) is twice as large with euDKA than with DKA.

It is the entity of glycosuria viz. the height of hyperglycemia that marks the difference between the two metabolic states.(DKA vs eDKA

- **Eu-DKA is a life-threatening emergency and need immediate evaluation and treatment.**

- **Eu-DKA is characterized by hyperglycemia with blood glucose levels <200 mg/dl.**

- **Eu-DKA can result in delayed diagnosis and treatment.**

- **Eu-DKA might occur not so infrequently in individuals treated with SGLT2i.**

Final Points

- Patients on SGLT2i may rarely develop EDKA, primarily due to certain predisposing factors, including severe acute infections and following major surgery.
- The signs and symptoms may be similar to DKA but with normal blood sugar levels, making the diagnosis challenging.
- Higher index of suspicion is warranted in such patients, as delay in diagnosis may lead to higher morbidity and mortality.
- EDKA outcomes are good if recognized timely and corrective actions are taken.
- Hence, physicians managing such patients must be aware of this potential complication and educate patients accordingly to ensure early diagnosis and management.


Re संस्कृत™
प्राता रत्नं प्रातरित्वा दधाति।
resanskrit.com
An early riser earns good health.
Rigveda1.125.1
प्रातःकाल उठने वाले अच्छा स्वास्थ्य प्राप्त करतें है।

अनुगृहीतोऽस्मि


धन्यवाद