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A Case Study of Euglycemic Diabetic Ketoacidosis

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ABSTRACT
Diabetic ketoacidosis (DKA), seen with relative frequency in the emergency department, is a potentially life-threatening complication of both type I diabetes mellitus and type II diabetes mellitus (T2DM) characterized by hyperglycemia, ketosis, and acidosis. However, an uncommon variation of DKA, termed euglycemic diabetic ketoacidosis (euDKA) has been increasing in frequency due to the abundance of patients with T2DM being managed on sodium-glucose cotransporter-2 inhibitors, which pose an increased risk of euDKA. The diagnosis of euDKA can be elusive as the typical presentation of substantial hyperglycemia is absent, which can lead to delayed diagnosis and treatment. This case study highlights the clinical presentation and management of euDKA patients to help increase awareness. **Key words:** diabetes mellitus management, euglycemic diabetic ketoacidosis, sodium-glucose cotransporter-2 inhibitors

CASE PRESENTATION

A 41-year-old male with past medical history significant for type II diabetes mellitus (T2DM), anxiety, and insomnia presents to the emergency department (ED) with flulike symptoms. He states his symptoms began 2 days ago with generalized weakness, fatigue, headache, body aches, chills, and nasal drainage. States vomiting and diarrhea began today. Reports upper abdominal "tenderness 'that he describes as a' burning" sensation. States he has had a couple episodes of diarrhea today that have been non-bloody. Reports a four episodes of vomiting today, also non-bloody. Denies trying any over-the-counter medications. States nothing seems to help his symptoms. Reports worsening of symptoms with eating and/or drinking. States he takes dapagliflozin (Farxiga) and sitagliptin/metformin (Janumet) for T2DM. In addition, the patient states he takes semaglutide (Ozempic), but reports he has been out of this medicine for the past month. Remote history of appendectomy and cholecystectomy.

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PHYSICAL EXAMINATION

Vital signs: Temperature oral 97.9 degrees Fahrenheit, pulse rate 90 bpm, respiratory rate 16 breaths/minute, blood pressure 124/

93 mm Hg, SpO_2 96% on room air. Measurements: Height/length measured 68.90 inches, weight dosing 103 kg, BMI 34.4. General: Alert, no acute distress. Skin: Warm, dry, normal for ethnicity. Head: Normocephalic. Neck: Supple,trachea midline. Eye: Extraocular movements are intact, normal conjunctiva. Ears, nose, mouth, and throat: Oral mucosa moist. Cardiovascular: Regular rate and rhythm, normal peripheral perfusion, no edema. Respiratory: Lungs are clear to auscultation, respirations are non-labored, breath sounds are equal,symmetrical chest wall expansion. Gastrointestinal: Soft, nontender, non distended, no organomegaly. Guarding: Negative. Rebound: Negative. Back: Normal range of motion. Musculoskeletal: Normal ROM. Neurological: Alert and oriented to person, place, time, and situation. No focal neurological deficit observed. Lymphatics: No lymphadenopathy. Psychiatric: Cooperative, appropriate mood, and affect.

DIFFERENTIAL DIAGNOSIS

Nausea, vomiting, abdominal pain, gastroenteritis, unstable angina, acute myocardial infarction, food toxicity, gastritis, pancreatitis, hepatitis, renal colic, dehydration, electrolyte abnormality, diverticulitis, viral syndrome.

LABORATORY AND DIAGNOSTIC FINDINGS

WBC 8.8 × 10^3/mcL, RBC 5.55 × 10^6/mcL, Hg 16.0 gm/dL, Hct 47.4%, MCV 85.5 fL, MCH 28.9 pg, MCHC 33.8 gm/dL, RDW 14.4%, Platelets 296 × 10^3/mcL, MPV 8.1 fL, Neutrophils 87.7%, Lymphocytes 5.3%, Monocytes 6.6%, Eosinophils 0.1%, Basophils 0.3%, neutro absolute 7.7 × 10^3/mcL, lymph absolute 0.5 × 10^3/mcL, mono absolute 0.6 × 10^3/mcL, Eos absolute 0.00 × 10^3/mcL, Baso Absolute 0.0 × 10^3/mcL, Sodium Lvl 135 mmol/L, Potassium Lvl 4.7 mmol/L, Chloride 103 mmol/L, CO_2 18 mmol/L, AGAP 21.0 mmol/L, BUN/creat ratio 14, BUN 17 mg/dL, Glucose Lvl 149 mg/dL, Creatinine Lvl 1.25 mg/dL, eGFR 74 mL/min/1.73 m^2, Calcium Lvl 9.4 mg/dL, Albumin Lvl 4.1 gm/dL, total protein 8.4 gm/dL, ALT 26 Intl Units/L, AST 22 Intl Units/L, Alk Phos 106 Intl Units/L, Bili Total 0.44 mg/dL, Magnesium Lvl 1.8 mg/dL, Lipase Lvl 11 Intl Units/L, lactic acid Lvl 0.8 mmol/L, Osmolality 274 mOsm/kg, HS Troponin <4, ng/L, Flu A Negative, Flu B Negative, SARS-coV-2 Negative.

COMPUTED TOMOGRAPHY ABDOMEN AND PELVIS WITHOUT CONTRAST

1. Slight prominence of multiple small bowel loops. This could indicate mild enteritis in the appropriate clinical setting. No evidence for mechanical bowel obstruction.
2. No other significant finding within the abdomen or pelvis.
3. Incidental finding of bilateral gynecomastia.

MANAGEMENT

Computed tomography findings consistent with mild enteritis. Patient was afebrile, nontoxic, and well-appearing. Serial abdominal exams revealed a soft and nontender abdomen. Patient received a liter of fluid, 4 mg of ondansetron (Zofran) and 20 mg of famotidine (Pepcid) per intravenous (IV) infusion. The patient reported feeling better, just had some mild burning in his upper stomach. He was discharged home with medication, ondansetron (Zofran) and famotidine (Pepcid), to help with symptom control and primary care follow-up in 1–2 days. Patient was instructed to return to the ED with any new or worsening symptoms.

OUTCOME

The patient returned to the ED the following day with abdominal pain, nausea, vomiting, and diarrhea. States despite taking prescribed ondansetron (Zofran) and famotidine (Pepcid), he has had worsening

Table 1. Current list of FDA-approved sodium glucose co-transporter 2-inhibitors

Generic drug name	Trade drug name
Canagliflozin	Invokana
Dapagliflozin	Farxiga
Empagliflozin	Jardiance
Ertugliflozin	Steglaro
Canagliflozin and metformin	Invokamet
Dapagliflozin and metformin extended release	Xiduo XR
Empagliflozin and linagliptin	Glyxambi
Empagliflozin and metformin	Synjardy

[AQ1]

of symptoms. He now has diffuse abdominal cramping and has had several episodes of non-bloody, nonbilious vomiting, and non-bloody diarrhea. Denies any prior history of diabetic ketoacidosis (DKA); glucose 263 at the time of ED arrival. Last emesis was 2 hr prior to ED arrival. Labs revealed lactic acid of 2.5, WBC 15.0 × 10^3/mcL, sodium Lvl 137 mmol/L, potassium Lvl 5.2 mmol/L, chloride 106 mmol/L, CO_2 <5 mmol/L, AGAP >26.0 mmol/L HI, creatinine Lvl 1.77 mg/dL.

The patient was diagnosed with euglycemic diabetic ketoacidosis (euDKA) and admitted to the intensive care unit. He was given Dextrose 5% with 0.9% NaCl and KCl 20 mEq/L IV solution 1,000 mL, along with insulin as needed and improved within 24 hr and was discharged home with complete resolution of symptoms.

EPIDEMIOLOGY AND PATHOGENESIS

While DKA is a common condition encountered in the ED, euDKA is a rare but potentially life-threatening condition that can be easy to overlook due to its lack of hyperglycemia. Euglycemic DKA is primarily caused by an imbalance between insulin and counterregulatory hormones, leading to increased ketone production despite normal or only mildly elevated blood glucose levels (Nasa, Chaudhary, Shrivastava, & Singh, 2021). The incidence of euDKA has been increasing, especially with the widespread use of sodium-glucose cotransporter-2 inhibitor (SGLT-2i). The use of SGLT-2i, a class of medications (see Table 1) that promote urinary glucose excretion, is a significant precipitating factor for euDKA (Nasa et al., 2021). While generally well-tolerated, SGLT-2i can predispose patients to euDKA, particularly in situations of reduced insulin secretion or increased insulin resistance. These drugs can reduce blood glucose levels without directly affecting insulin secretion or action, potentially leading to a relative insulin deficiency state. Other contributing factors to euDKA may include reduced food intake or fasting, alcohol consumption, surgery, infections, and underlying insulin deficiency or resistance (Sell, Haas, Korley, Cranford, & Bassin, 2023). The combination of these factors can disrupt glucose metabolism, promote lipolysis, and increase ketone body production, resulting in the development of euDKA.

PRESENTATION AND SYMPTOMS

Euglycemic DKA and hyperglycemic DKA present with distinct clinical features despite both involving ketoacidosis. In euDKA, patients commonly experience symptoms such as nausea, vomiting, abdominal pain, and altered mental status (Plewa et al., 2023). [AQ2] Notably, blood glucose levels remain within the normal range or are only mildly elevated, while ketone levels are elevated, reflecting the predominant metabolic disturbance. Hyperglycemic DKA is characterized by hyperglycemia (blood glucose >250 mg/dL), ketosis, metabolic acidosis, and dehydration (Shah, Pathrose, Bhagwat, & Chandy, 2022). Patients with hyperglycemic DKA often exhibit classic signs of diabetes mellitus (DM), including polyuria, polydipsia, fruity breath odor due to acetone exhalation, and profound fatigue due to metabolic derangements

Table 2. Laboratory values in diabetic ketoacidosis (DKA), and euglycemic DKA (representative ranges at presentation)

	DKA	EUGLYCEMIC DKA[a]
Glucose,[b] mmol/L (mg/dL)	13.9–33.3 (250–600)	<11.1–13.9 (<200–250)[a]
Sodium, meq/L	125–135	~135
Potassium[b,c]	Normal to ↑	Normal to ↑
Magnesium[b]	Normal	Normal
Chloride[b]	Normal	Normal
Phosphate[b,c]	Normal	Normal
Creatinine	Slightly to moderately ↑	Slightly ↑
Osmolality (mOsm/mL)	300–320	~300
Serum/urine ketones[b]	++++	++++
Serum β-hydroxybutyrate, mmol/L	>2.5	>2.5
Serum bicarbonate,[b] meq/L	<18	<18
Arterial pH	6.8–7.3	6.8–7.3
Arterial PCO_2,[b] mm Hg	20–30	20–30
Anion gap[b]($Na—[Cl + HCO_3]$)	↑	↑

Note. Adapted from *Harrison's Principles of Internal Medicine* (21st ed., eBook). By J. Loscalzo, A. Fauci, D. Kasper, S. Hauser, D. Longo, and J. L. Jameson, 2022, McGraw Hill, LLC. Copyright 2022 by McGraw Hill, LLC. Reprinted with permission.

[a]Sometimes occurs with SGLT2 inhibitor treatment; disproportionate glucosuria is consistent with SGLT2 inhibitor effect.

[b]Large changes occur during treatment of DKA.

[c]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.

and dehydration. These differences in presentation highlight the importance of considering both blood glucose levels and ketone levels in the differential diagnosis of ketoacidosis in patients with DM.

LAB TESTING AND DIAGNOSIS

When diagnosing euDKA, healthcare providers rely on a combination of clinical judgment, laboratory tests, and metabolic parameters. Evaluation should include presenting signs and symptoms, blood ketone levels (>3 mmol/L), metabolic acidosis indicated by a low pH (<7.3) and bicarbonate levels (<18 mEq/L), and the presence of normal or slightly elevated blood glucose levels. Hyperglycemic DKA is characterized by hyperglycemia, the presence of ketones in the blood (ketonemia) or urine (ketonuria), metabolic acidosis, and any electrolyte imbalances, which can be detected through an elevated anion gap (Nasa et al., 2021). These diagnostic criteria help healthcare providers differentiate between euDKA and hyperglycemic DKA based on the specific metabolic derangements present in each condition (see Table 2).

MEDICAL MANAGEMENT PROTOCOL

The management of euglycemic euDKA follows a similar approach to classic DKA, which involves addressing dehydration and ketosis. The management of euDKA requires vigilance to avoid hypoglycemia while treating ketosis with an IV insulin infusion (Sell et al., 2023). Since euDKA is characterized by blood glucose levels below 250 mg/dL, IV fluids containing dextrose are administered along with insulin to prevent hypoglycemia (Klinkner et al., 2023). Insulin plays a crucial role in suppressing ketone production and correcting metabolic acidosis (Klinkner & Steingraber-Pharr, 2023). Monitoring and

replenishing electrolytes as necessary (including potassium, sodium, and bicarbonate levels) and correcting dehydration are also important factors in euDKA management (Klinkner et al., 2023). Given that ketonuria is expected with SGLT-2i therapy, it's recommended to directly measure ß-hydroxybutyrate levels in the blood. If SGLT-2i were used prior to euDKA, they should be discontinued. The extended half-life of SGLT-2i, ranging from 11 to 17 hr, may prolong the requirement for IV insulin. Some case reports suggest that the glycosuric effects of SGLT-2i, can persist for up to 10–12 days post-discontinuation, increasing the risk of euDKA recurrence if insulin therapy is discontinued prematurely.

IMPLICATIONS FOR PRACTICE

Euglycemic DKA is a rare but potentially life-threatening complication in patients with DM, particularly patients with T2DM who are being treated with SGLT-2i. Clinicians should maintain a high index of suspicion for euDKA in diabetic patients presenting with symptoms suggestive of metabolic derangement, even in the absence of hyperglycemia (Klinkner & Steingraber-Pharr, 2023). Symptoms frequently include nausea, vomiting, and abdominal pain. In addition to baseline labs, workup should include blood ketone levels (>3 mmol/L) and an arterial blood gas with acidosis indicated by a low pH (<7.3) and bicarbonate levels (<18 mEq/L) (Long, Lentz, Koyfman, & Gottlieb, 2021). Prompt recognition and appropriate management, including IV fluid resuscitation, insulin therapy, and electrolyte repletion are crucial for favorable outcomes. This case underscores the importance of a comprehensive approach to the management of euDKA to mitigate morbidity and mortality associated with this condition. Currently, euKDA accounts for only 2.6%–3.2% of ED DKA admissions, however this number is likely to increase since the American Heart Association guidelines recently endorsed SGLT2-i as a Class 1 recommendation for patients with heart failure (Sell et al., 2023).

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