T1D Preventing and Managing Diabetic Ketoacidosis in People with T1D

FACULTY

Steven V. Edelman, MD
Clinical Professor of Medicine
UC San Diego School
    of Medicine
Founder and Director
Taking Control of Your Diabetes
Solano Beach, CA

WRITER

Katherine Kahn
Holyoke, MA

ACTIVITY PLANNERS

Jaime Symowicz, PhD
Manager, Educational Strategy
    and Content
Med-IQ
Baltimore, MD

Lisa R. Rinehart, MS, ELS
Director, Editorial Services
Med-IQ
Baltimore, MD

Samantha Gordon
CME Specialist
Med-IQ
Baltimore, MD

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Diabetic ketoacidosis (DKA) is a potentially life-threatening complication for any person with type 1 diabetes (T1D).[1] However, advances in DKA prevention, earlier recognition, and better treatments have substantially diminished hospitalizations and overall mortality rates associated with the condition.[2,3] This publication reviews the basics of DKA and explores how healthcare providers can help their patients with T1D take a proactive role in its detection and management.

WHAT IS DKA?

DKA is a hyperglycemic state characterized by metabolic acidosis and ketosis.[4] Rarely, DKA can also occur in euglycemic states (glucose less than 250 mg/dL, euDKA).[5] It occurs in the setting of absolute or relative insulin deficiency in combination with an increase in counterregulatory hormones, such as glucagon, cortisol, catecholamines, and growth hormone.[3]

The prevalence of DKA in T1D ranges from approximately 1.3% in those with a hemoglobin A1c (HbA1c) below 7% to nearly 16% in individuals with poorly controlled glycemia (ie, HbA1c of 9% or higher).[6]

Precipitating factors associated with DKA in T1D include[1,2,4]:

- Illness (eg, infection, pancreatitis, myocardial infarction, cerebrovascular accident)
- Discontinuation of or inadequate insulin therapy (eg, poor adherence, pump therapy malfunction [typically infusion line disruption], inappropriate dose reduction)
- Not making appropriate insulin adjustments during pregnancy
- Substance abuse (eg, alcoholism, recreational drug use)
- Medications that alter carbohydrate metabolism (eg, corticosteroids, atypical antipsychotics, thiazide diuretics, beta-blockers, sodium-glucose cotransporter 2 [SGLT2] inhibitors)
- Hyperthyroidism
- Trauma

> **DEFINITION OF DKA**
>
> The combination of:
> - Ketonuria or ketonemia
> - Serum glucose > 250 mg/dL
> - Arterial pH < 7.3
> - Bicarbonate < 15 mEq/L

EARLY SIGNS AND SYMPTOMS

DKA usually evolves quickly, often over several hours.[1] Affected patients have typical symptoms of hyperglycemia (eg, polyuria, polydipsia, polyphagia) and a variety of other signs and symptoms, such as[1]:

- Nausea/vomiting
- Dehydration
- Weakness
- Abdominal pain
- Altered mental status/coma

Physical examination may reveal tachycardia, hypotension, and hypothermia.[7] Poor skin turgor and dry mucus membranes secondary to dehydration may also be observed. Patients may also have a fruity breath odor related to acetone production or exhibit Kussmaul respirations.[7]

Euglycemic DKA

EuDKA is defined as serum glucose lower than 250 mg/dL but with a high anion gap metabolic acidosis and positive serum or urine ketones.[5] Because of normal or modestly elevated blood glucose levels, the diagnosis of euDKA can be challenging, and treatment is often delayed.[5,8] Therefore, providers should maintain a high clinical index of suspicion of euDKA in patients with T1D, even if their blood glucose is normal.[5] Contributing factors to the onset of euDKA in patients with T1D include vomiting, fasting, or recent insulin administration.[3] The off-label use of SGLT2 inhibitors in patients with T1D has also been associated with euDKA.[3]

DKA PREVENTION: PATIENT EDUCATION

Patients with T1D should be taught to measure urinary ketones (with ketone strips) or blood ketones (with a ketone meter) whenever they have symptoms consistent with DKA, which can often masquerade as the flu, regardless of blood glucose concentration.[9]

Urine ketone strip testing[9]:
- Represents only an average of urine ketone concentration since the last void
- Has a lower sensitivity and specificity for DKA than blood ketone measurement
- Detects acetoacetic acid only, not β-hydroxybutyrate, the main metabolite in ketoacidosis
- Can be simple and inexpensive

Blood ketone meter testing[10]:
- Detects β-hydroxybutyrate, the main metabolite in ketoacidosis
- Has no time lag and is more accurate than urine testing
- Works the same way that a blood glucose meter does (some ketone meters can also measure blood glucose levels, but with different test strips)
- Is more expensive than urine strips

For a definitive diagnosis of DKA in the clinic, the direct measurement of serum β-hydroxybutyrate is the preferred laboratory method.[7]

Insulin Pumps and DKA

> **A 14-year-old girl with T1D presents with nausea, vomiting, weakness, abdominal pain, trouble breathing, and confusion. Her endocrinologist had initiated insulin pump therapy 10 days ago, but her parents say that they have had a difficult time figuring out how to use it.**

Patients using insulin pumps may have a greater risk of DKA.[7] It can manifest rapidly if the pump is disconnected for more than 1 to 2 hours, if the pump malfunctions (less common), or if there are problems with the infusion set (more common).[11] The following patient education sheet is an example of what individuals starting initial pump therapy need to know about DKA.[11]

PREVENTING DKA WHEN USING AN INSULIN PUMP

If blood glucose is higher than 250 mg/dL:
- ▶ Check to make sure the pump, infusion set, tubing, and reservoir/cartridge are working correctly
- ▶ If the pump/infusion set is working correctly, give a correction bolus with the pump
- ▶ Check blood glucose in 1 hour

If blood glucose is still high (> 250 mg/dL) 1 to 2 hours after the correction bolus:
- ▶ Check urine for ketones, or check blood with a ketone meter
- ▶ Recheck the infusion set and site

If ketone levels are moderate (0.6-1.5 mmol/L) to high (> 1.5 mmol/L) or blood glucose is rising:
- ▶ Inject a correction dose of rapid-acting insulin by SYRINGE or PEN (not by pump)
- ▶ Change the pump cartridge, tubing, and infusion set, and use a new insulin vial
- ▶ Check blood glucose every hour until it returns to normal
- ▶ Drink plenty of noncaffeinated fluids to avoid dehydration
- ▶ Consume 30 grams of carbohydrate, and give the appropriate amount of insulin

Call your healthcare provider or go to the emergency department if you have high ketones, nausea and vomiting, or trouble breathing.

Adapted from University of Washington Medical Center. Insulin pumps and diabetic ketoacidosis (DKA). Last updated June 2013. https://healthonline.washington.edu/sites/default/files/record_pdfs/Insulin-Pumps-Diabetic-Ketoacidosis-(DKA).pdf. Accessed February 25, 2020; and Kwon J. Making sense of ketones with diabetes. DiaTribe Learn. https://diatribe.org/making-sense-ketones-diabetes. Accessed April 13, 2020.

DKA and SGLT2 Inhibitors

A 33-year-old man with T1D called his doctor because he suddenly began feeling fatigued and sick to his stomach. He tested his blood glucose and blood ketones at home; his blood glucose was 185 mg/dL, but his blood ketone level was 1.7 mmol/L. Recently, he was prescribed an SGLT2 inhibitor.

The off-label prescribing of SGLT2 inhibitors in T1D has become increasingly common, as an adjunct to insulin therapy when patients are not achieving glycemic goals.[8] Although several studies have found significant improvements in glycemic control in patients with T1D when an SGLT2 inhibitor was added to insulin therapy, these studies also revealed a small, but definite, dose-dependent increased risk of DKA in such situations.[12-16]

If the insulin dose is reduced excessively when starting an SGLT2 inhibitor, the risk of ketosis can increase.[17] These medications may also predispose individuals toward ketogenesis and acidosis via volume depletion and dehydration, sodium reabsorption in renal tubules that interferes with ketone excretion, and increased glucagon levels.[17]
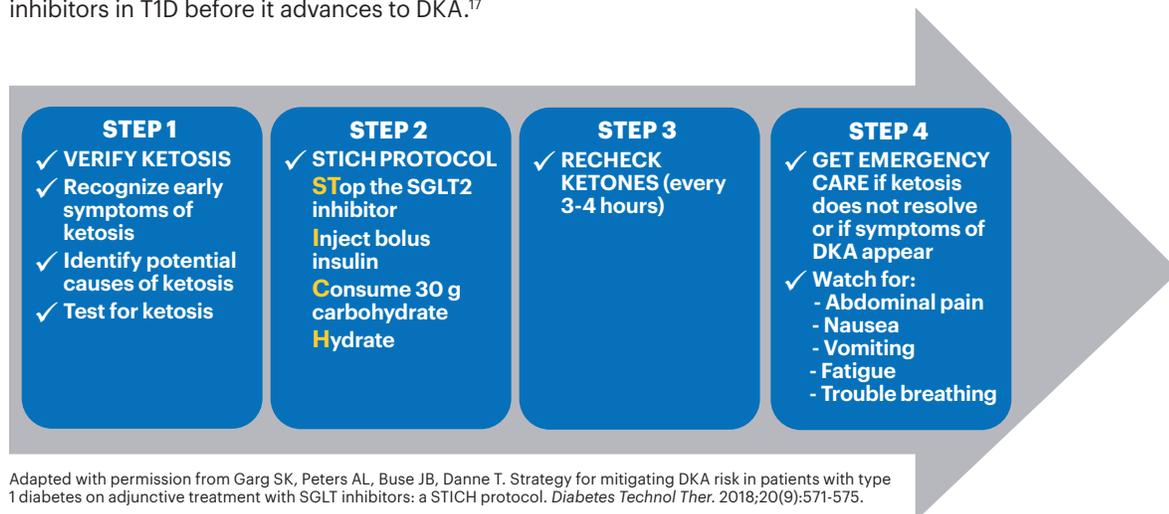
Patient selection. If clinicians decide to recommend an SGLT2 inhibitor off-label for a patient with T1D, they must carefully assess individual risk factors to mitigate the potential risk of DKA. Generally, SGLT2 inhibitors should be avoided or used cautiously in patients who[8]:

• Have recurrent episodes of DKA
• Have extended periods of hyperglycemia exceeding 350 mg/dL
• Have challenges following diabetes management plans
• Are inexperienced insulin pump users
• Follow low carbohydrate/ketogenic diets
• Consume excessive amounts of alcohol

Because pregnancy is associated with an increased risk of ketoacidosis, SGLT2 inhibitors should not be used in pregnant women with T1D.[8] Until data are available on the safety of SGLT2 inhibitors in children, these drugs should not be used in patients younger than 18 years.[8]

The STICH protocol (shown in step 2) is a tool that is part of a treatment plan that can be used to provide guidance to both clinicians and patients for recognizing and treating ketosis associated with the use of SGLT2 inhibitors in T1D before it advances to DKA.[17]

STEP 1	STEP 2	STEP 3	STEP 4
✓ **VERIFY KETOSIS** ✓ **Recognize early symptoms of ketosis** ✓ **Identify potential causes of ketosis** ✓ **Test for ketosis**	✓ **STICH PROTOCOL** **ST**op the SGLT2 inhibitor **I**nject bolus insulin **C**onsume 30 g carbohydrate **H**ydrate	✓ **RECHECK KETONES (every 3-4 hours)**	✓ **GET EMERGENCY CARE if ketosis does not resolve or if symptoms of DKA appear** ✓ **Watch for:** - Abdominal pain - Nausea - Vomiting - Fatigue - Trouble breathing

Adapted with permission from Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. *Diabetes Technol Ther.* 2018;20(9):571-575.

DKA AND SICK DAY MANAGEMENT

A 55-year-old woman with T1D (HbA1c of 9.2%) was found in an unresponsive state by her husband. When she presented at the emergency department, her husband explained that she had started with a "stomach flu" 2 to 3 days ago. She had been too sick to eat, so she had stopped taking her insulin.

Any type of illness, physical stress, emotional stress, or surgery can cause elevated cortisol and hyperglycemia in individuals with T1D, even in those who are not eating.[11] To prevent DKA, clinicians should provide all patients with a sick day plan, such as the below example.

SICK DAY PLAN FOR PEOPLE WITH T1D

Monitor
▶ Blood glucose every 2 hours
▶ Urine or blood ketones every 4 to 6 hours when sick (eg, flu, infection) and whenever blood glucose is above 240 mg/dL

Continue Insulin
▶ Doses may need to be adjusted during illness, depending on whether your are eating
▶ Discuss insulin dose changes with your healthcare provider

Prevent Dehydration
▶ Drink small amounts of fluids (water or other liquids) every 10 minutes
▶ Replace fluid losses from vomiting/diarrhea with sports drinks, juices, soups

Replace Complex Carbohydrates (if unable to eat solid foods)
▶ Choose foods containing sugar, such as:
  - Jello
  - Juices
  - Sports drinks
  - Soda
  - Popsicles
  - Sherbet/ice cream

Contact Healthcare Provider/Seek Emergency Care
▶ If blood glucose is above 250 mg/dL with a moderate to large amount of urine ketones
▶ If symptoms of DKA are present
▶ If blood glucose cannot be controlled

DKA TREATMENT

Treatment of DKA is best accomplished in an intensive care unit (ICU) or emergency department and is typically beyond the scope of primary care practice. The core of DKA treatment involves the correction of[18]:

- Fluid loss, with intravenous fluids
- Hyperglycemia, with IV insulin until ketosis subsides
- Electrolyte disturbances, especially potassium imbalances
- Acid-base imbalance

The American Diabetes Association published a DKA consensus statement in 2009 that includes detailed inpatient treatment recommendations.[4]

The treatment of precipitating illnesses, if present, is also an important consideration.[18] Identifying the initial cause of DKA is imperative, and addressing preventive measures through education is vital to avoid readmission. For patients who withhold their insulin secondary to an eating disorder or mental condition, psychological help is essential. Fortunately, most patients recover from DKA without residual health problems and should follow up with their healthcare provider within 1 month of discharge.[18]

ADDITIONAL RESOURCES

We hope you found this to be a useful summary of information to help you manage DKA in individuals with T1D. The following additional resources may be helpful:

- DKA consensus statement: https://care.diabetesjournals.org/content/32/7/1335
- Taking Control of Your Diabetes (TCOYD) patient education video (Everything You Need to Know About DKA): https://tcoyd.org/2019/04/everything-you-need-to-know-about-dka/

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