# Too much of a good thing

## *Management of diabetic ketoacidosis in adults*

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*A healthy 19-year-old man presents to your emergency department complaining of weakness and lethargy for the past 2 weeks. He sleeps 10 hours a day, yet remains tired. His appetite has been poor and he constantly feels thirsty. He voids frequently with no dysuria or hematuria. For the past 24 hours, he has been experiencing moderately severe and diffuse abdominal pain; he vomited 4 times in the past 2 hours. He has lost 10 kg over the past 2 weeks. He denies other symptoms or using drugs or medications, and he drinks alcohol only socially. His personal and family medical histories are not relevant.*

*An examination reveals blood pressure of 115/60 mm Hg, heart rate of 135 beats per minute, temperature of 36.9°C, respiration rate of 24 breaths per minute, and oxygen saturation of 100% on room air. The patient is alert and appears uncomfortable, retching repeatedly. The mucosae are dry and the abdomen soft but diffusely tender, with normal bowel sounds and no peritoneal signs. There is no costovertebral angle tenderness. Findings from the remainder of the examination are noncontributory.*

*A bedside glucometer displays "High-High-High." Laboratory investigations reveal a white blood cell count of 14.2×10⁹/L, a hemoglobin level of 143 g/L, a platelet count of 365×10⁹/L, a sodium level of 133 mmol/L, a potassium level of 2.9 mmol/L, a chloride level of 103 mmol/L, a blood urea nitrogen level of 17 mmol/L, a creatinine level of 144 µmol/L, a glucose level of 29.7 mmol/L, an arterial pH of 7.10, a $Pco_2$ of 23 mm Hg, a $Po_2$ of 95 mm Hg, a bicarbonate level of 11 mmol/L, and an oxygen saturation of 95%. Urinalysis results are positive for high levels of ketones and glucose. How would you approach this patient?*

Diabetic ketoacidosis (DKA) occurs in 4.6 to 8 of 1000 diabetic patients.[1] Up to 20% of patients present without a previous diagnosis of diabetes.[1] Primarily thought of as a complication of type 1 diabetes, DKA is increasingly noted in type 2 diabetes.[1] Mortality ranges from 0.65% in young patients to greater than 25% in patients older than 70 years.[1-3]

## Pathophysiology

The underlying mechanism of DKA is a reduction in the effective concentration of circulating insulin, coupled with a concomitant elevation of counterregulatory stress hormones. When insulin is decreased, hyperglycemia develops as a result of increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose use by peripheral tissues.

The increased production of ketones results from the breakdown of triglycerides into glycerol and free fatty acids, which are then oxidized to ketones (β-hydroxybutyric acid and acetoacetic acid). In DKA, the ratio of β-hydroxybutyric acid to acetoacetic acid increases to as much as 10:1, leading to an underestimation of ketones if the β-hydroxybutyric acid is not measured.[3] In addition to their increased production, ketone clearance also appears to be affected in DKA.[4]

## Diagnosis

There are no definitive criteria for the diagnosis of DKA.[2] Typically, the arterial pH is less than 7.3, serum bicarbonate levels are less than 15 mmol/L, and the anion gap is greater than 12 mmol/L, with positive serum or urine ketones. Plasma glucose levels are usually greater than 14.0 mmol/L, but they can be lower.[2]

The ketoacids cause increased anion gap metabolic acidosis. The nitroprusside reaction typically used to measure ketones provides a semiquantitative estimation of acetoacetate and acetone only, resulting in an underestimation of the severity of ketoacidosis.[1] Direct measurement of β-hydroxybutyric acid levels is preferable.

## Treatment

The use of standardized treatment protocols has improved care and decreased morbidity.[5,6] The Canadian Diabetes Association publishes guidelines and treatment algorithms every 5 years on the management of DKA. The therapies highlighted below reflect the current Canadian recommendations.[2] The mainstays of treatment are 1) fluid replacement, 2) correction of potassium deficit, 3) correction of metabolic acidosis, and 4) treatment of precipitating factors.

***Fluid replacement***. Hyperglycemia leads to osmotic diuresis, with loss of water exceeding that of sodium.[4] In addition, ketone excretion forces the excretion of sodium, potassium, and ammonium. The typical water loss amounts to 5 to 7 L.[4]

Aggressive rehydration lowers serum glucose independently of insulin, decreases the levels of counterregulatory hormones, restores intravascular volume, and reduces the insulin resistance caused by the DKA hyperosmolar state.[3] Start with 1 to 2 L/h of

normal saline solution to correct shock, followed by 0.5 L/h of normal saline solution for 4 hours, and then decrease the rate to 250 mL/h. Add 5% dextrose in water (D5W) when serum glucose levels reach 14 mmol/L in DKA so that insulin can be continued to achieve ketone clearance.[2]

***Correction of potassium deficit.*** Diabetic ketoacidosis is associated with profound body potassium depletion, ranging from 3 to 15 mmol/kg, in spite of an initial plasma concentration typically normal or elevated at presentation.[4] Potassium follows water as it shifts out of cells; acidosis further enhances this shift. In addition, the lack of insulin impairs potassium entry into cells.[4] Ketone excretion accelerates the potassium loss owing to osmotic diuresis. Although treatment with hydration and insulin leads to a rapid decrease in potassium, replacement should not be started until the potassium level is less than 5.0 to 5.5 mmol/L and diuresis is well established.[2,4] If the patient is normokalemic or hypokalemic at presentation, potassium should be given immediately at 10 to 40 mmol/L, at a maximum rate of 40 mmol/h.[2] In the case of frank hypokalemia (potassium level <3.3 mmol/L), insulin should be withheld until potassium replacement at 40 mmol/h has restored potassium to greater than 3.3 mmol/L.[2,4] Electrolyte levels must be monitored every 2 to 4 hours.

***Correction of metabolic acidosis***

*Insulin:* As presented above, serum potassium levels should be checked and corrected to greater than 3.3 mmol/L before starting insulin.[2]

A bolus dose of insulin appears to be unnecessary and is no longer recommended if the infusion rate is at least 0.1 U/kg/h.[7-10]

Serum glucose needs to be monitored every 1 to 2 hours. The target is a decrease of 3 to 4 mmol/L in the first hour (increase drip if necessary)[2,4]; a steeper decrease in hyperosmolarity might be associated with a higher risk of cerebral edema. Decrease the infusion by 50% when serum glucose levels reach 14 mmol/L and add D5W, aiming for a level between 12 and 14 mmol/L. Continue insulin until DKA is resolved (bicarbonate >18 mmol/L, anion gap ≤12 mmol/L, and pH >7.3).

*Bicarbonate:* Alkali therapy is usually not necessary because metabolic acidosis tends to be corrected with insulin therapy. The administration of bicarbonate might actually lead to rebound alkalosis, worsened hypokalemia, paradoxical central nervous system acidosis, an increase in intracellular acidosis, and prolongation of ketosis.[3] Because severe acidosis might lead to important adverse side effects, and because of the small number of patients with a pH less than 7.0 included in most studies, bicarbonate therapy seems prudent if the pH is less than 7.0. Use 100 mmol (2 ampules) of bicarbonate in 400 mL of sterile water with 20-mmol/L potassium chloride at 200 mL/h until the pH is greater than 7.0.[2]

***Treatment of precipitating factors.*** The 2 main precipitating factors are infections (up to 60% of cases, with pneumonia and urinary tract infections accounting for 30% to 50% of cases) and omission of or undertreatment with insulin (20% to 40%).[1,3,4] Drugs such as β-blockers, calcium channel blockers, diuretics, loxapine, phenytoin, steroids, and cocaine are also common triggers.[1,3]

## Pediatric considerations

This article focuses on the treatment of adult DKA. Although the pediatric principles are similar, most pediatric centres have strict protocols and they should be consulted before initiating treatment.

## Complications of treatment

***Hypoglycemia.*** Hypoglycemia is especially common if an insulin bolus has been administered.

***Cerebral edema.*** Cerebral edema is more common in children, especially children newly diagnosed with diabetes. The mortality rate is 20% to 40%. There is controversy regarding whether the condition is present before initiation of treatment or whether it is related to the rapid change in osmolarity.

***Adult respiratory distress syndrome.*** Adult respiratory distress syndrome is rare. Fluid intake should be limited in patients with rales or increased alveolar-arterial $Po_2$ gradients.

*Your patient was diagnosed with DKA and new-onset type 1 diabetes. After 8 hours of fluid and insulin therapy, half of his fluid deficit had been restored and his serum glucose was maintained at 12 mmol/L with D5W and continuous insulin. His abdominal pain and nausea have resolved.*

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**Competing interests**
None declared

**BOTTOM LINE**

- Diabetic ketoacidosis is increasingly seen in patients with type 2 diabetes.
- Treatment should be initiated with 1 to 2 L of normal saline solution over the first hour. Serum potassium must be greater than 3.3 mmol/L before insulin is started. Boluses of insulin are no longer recommended.
- Reserve treatment with bicarbonate for patients with pH less than 7.0.

## POINTS SAILLANTS

- On observe de plus en plus de cas d'acidocétose diabétique chez les patients atteints de diabète de type 2.
- Il faut initier un traitement au moyen de 1 à 2 litres de solution saline normale pendant la première heure. Le potassium sérique doit excéder 3,3 mmol/l avant de commencer l'administration d'insuline. Les bolus d'insuline ne sont plus recommandés.
- Réservez le traitement au bicarbonate aux patients dont le pH est de moins de 7,0.

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