Diabetic ketoacidosis: principles underlying initial fluid management

Panduka Karunanayake
Department of Clinical Medicine, Faculty of Medicine, University of Colombo

Diabetic ketoacidosis (DKA) is a medical emergency that used to be uniformly fatal before insulin therapy became available. However, although its primary lesion is absolute or relative severe insulin deficiency ('insulinopenia'), it gives rise to most of its manifestations and fatalities through derangements in the volume and the composition of body fluid compartments. Therefore, correct management of DKA requires an awareness of its 'abnormal biochemistry' and optimum method for its correction. This article attempts to summarize these aspects of DKA.

At the end of this article you should be able to:

1. Outline the pathophysiology of the body fluid compartment derangements in DKA.

2. Relate this knowledge to the clinical and laboratory abnormalities that are used in clinical practice in diagnosis and assessment of DKA.

3. Outline the principles of initial management of the above derangements.

In addition, during your ward work you should be able to acquire abilities to:

1. Differentiate DKA from other conditions that have a similar clinical and/or biochemical presentation.

2. Assess the DKA patient using clinical methods and available laboratory tests to obtain information necessary for management.

3. Tailor the DKA management regimen/s to suit the individual patient.

It is important to keep in mind that the overall management of the DKA patient includes other important aspects that are not specifically covered in this article.

These include:

1. A search for precipitating causes.
2. A search for complications of DKA as well as their treatment.
3. Insulin therapy.
4. Switch over to medium- and long-term management at appropriate times.
5. Explanation to patient and relatives.

Introduction

The sine-quo-none of DKA is severe insulin deficiency combined with a stress response:

1. There is absolute or relative insulin deficiency.

2. There is an excessive stress response, which is evident as increased actions of counter-regulatory hormones (such as glucagon, cortisol, catecholamines, and growth hormone). Patients who have an insulinopenia do not invariably progress to DKA; they generally need an additional 'stress factor' or precipitating factor in addition (such as infection, acute myocardial infarction, acute pancreatitis, or surgery).

These lead to the important endocrine/metabolic effect of a shift of the intermediary metabolism away from 'storage' (anabolism) to 'usage' (catabolism): there is utilization of metabolic substrates for the production of glucose and ketone bodies (glycogenolysis, gluconeogenesis, and lipolysis), even while the tissues are unable to utilize the glucose so produced (since glucose cannot enter cells because of the lack of insulin).

The triad in DKA is:

HYPERGLYCAEMIA (other conditions in which this occurs are uncontrolled diabetes mellitus, hyperglycaemic hyperosmolar state, and stress hyperglycaemia).

KETONAEMIA, which is detected as ketonuria (other conditions in which this occurs are starvation, alcohol intoxication, hyperemesis, and ketotic hyperglycaemia).

METABOLIC ACIDOSIS with a high anion gap (other conditions in which this occurs include lactic acidosis, uraemic acidosis, methanol poisoning, and salicylism).

Pathogenesis of DKA

1. Gluconeogenesis, glycogenolysis, and reduced peripheral utilization of glucose lead to hyperglycaemia. Once it exceeds the renal threshold for glucose reabsorption (which is usually about 180 mg/dL), glycosuria starts.

2. The glycosuria leads to osmotic diuresis and polyuria. Furthermore, the presence of an excess osmole in the renal tubular lumen (namely, glucose) leads to retention of water in it and hence dilution of solutes, including sodium. This in turn leads to the setting up of a chemical concentration gradient for sodium across the renal tubular cell, leading to loss of sodium (along with chloride and more water). The resultant extra-cellular fluid (ECF) depletion stimulates the renin-angiotensin-aldosterone mechanism, which attempts to reduce sodium loss by exchanging some of it with potassium and hydrogen ions in the distal convoluted tubule. All these give rise to dehydration with loss of sodium, chloride and potassium.

3. The dehydration is further aggravated by the ketone bodies, because this leads to ketonuria, leading to further loss of sodium and osmotic loss of water. (Ketone bodies can exist as acids or the corresponding sodium salts: eg, β-hydroxy-butyric acid and sodium β-hydroxy-butyrate.) The accumulation of ketones in the ECF leads to a high anion gap metabolic acidosis.

4. The loss of fluid and the accumulation of osmoles (glucose and ketone bodies) in the ECF increase its osmolality, leading to osmosis of water out of the intra-cellular fluid (ICF) compartment. The cells compensate for this extra-cellular hypertonicity by generating and retaining intra-cellular osmoles, so that this osmosis is reduced.

5. Proteolysis releases bound cellular potassium into the ICF. This potassium then leaves cells because insulin is required to keep them in the cells, and the extra-cellular acidosis further promotes ICF potassium loss. As a result, the ICF potassium and water enter the ECF, and they are then lost from the ECF via the kidneys (along with sodium and chloride).

6. The result is severe depletion of sodium, chloride, potassium and water from the body, resulting in severe dehydration (over 6 L of fluid) and accumulation of ketoacids and glucose in the ECF, leading to hypertonicity. The ECF bears severe sodium, chloride, and water loss with accumulation of glucose and ketoacids, while the ICF bears severe potassium and water loss. Other electrolytes are also lost due to polyuria, including calcium, phosphate and magnesium; in addition there is massive calorie loss as a result of uncontrolled catabolism which, along with the dehydration, leads to weight loss.

The deleterious effects of this situation are as follows:

1. The most serious and life-threatening effect is severe dehydration. In addition to the above reasons, it may be aggravated by fever, vomiting, diarrhoea, and diuretic use. Dehydration leads to hypotension, poor tissue perfusion, and organ failure. It is important to note that insulin therapy in the presence of dehydration can cause further hypotension and worsening of the clinical situation; it is therefore important to ensure

that fluid resuscitation is already commenced and in progress before commencing insulin therapy. *In DKA what kills is the dehydration, not the insulinopenia.*

2. The acidosis and electrolyte imbalances (especially potassium) can also be life-threatening. The severity of the DKA can be measured by the severity of the acidosis, and this is closely followed by deterioration in the level of consciousness (see table1.)

Table 1: Grading DKA severity according to level of acidosis

	Mild	Moderate	Severe
Arterial pH	7.25 - 7.30	7.00-7.24	<7.0
Arterial HCO_3	15 – 18	10-14	<10
Level of consciousness	Alert	Alert → drowsy	Drowsy → coma

Principles of fluid management

1. Commence rehydration immediately and briskly. This is commenced with 1 L (about 15-20 mL/kg body weight) of normal saline in the first one hour. Under optimum conditions, we should have serum sodium, potassium, chloride, bicarbonate, urea and creatinine concentrations as well as arterial blood gas analysis at the end of the first hour.

2. From the second hour, we should be able to commence insulin therapy as well as continue fluid resuscitation.

3. The type of fluid (whether normal or half-normal saline) and the need for adding potassium to the fluids can be decided now, and the rate of subsequent fluid infusion can be determined according to the patient's co-morbidities (especially heart disease, which if present should lead to a slower rate).

4. Insulin has two desired effects: reversal of hyperglycaemia (which occurs promptly), and elimination of ketone bodies (which requires prolonged insulin administration). Initially, β-hydroxy-butyrate becomes converted to acetoacetate, and since the latter (and not the former) gives a positive result in tests using the nitroprusside method, such tests may increase in positivity whether or not the condition is improving with treatment.

5. The type of fluid is changed from saline to dextrose-water once the blood glucose is about 200 mg/dL. This is because of (at least) two reasons:

   a. By this time the fluid deficit has been mostly replaced, so that there is less urgent need for saline.

   b. We need to continue insulin infusion in spite of a reasonable blood glucose, because of the need to give insulin until the ketonaemia has resolved. In this setting, dextrose solution will have the advantage of preventing hypoglycaemia due to the insulin infusion.

6. Serum potassium is replenished intra-venously. It is important to ensure that the patient continues to have a urine output of at least 50 mL/hour while potassium is being given IV. It is given as follows:

   a. Serum K >5 KCl is not given

   b. Serum K 4-5 KCl 20 meq/L

   c. Serum K 3-4 KCL 40 meq/L

   d. Serum K <3 stop insulin → give KCl 10-20 meq/hour until serum K >3.3 meq/L → then give KCl 40 meq/L → restart insulin

7. Acidosis is treated only if it is severe, since treatment with $NaHCO_3$ has deleterious effects too (eg, paradoxical worsening of intra-cellular acidosis, worsening hypokalaemia). When the pH is <7.0, the possibility of impaired myocardial contractility is significant, and $NaHCO_3$ is therefore given (but only to raise the pH to 7.0). It is given as follows:

   a. If arterial pH <7.0 and HCO_3 <5 mmol/L, give $NaHCO_3$ 50 meq in 200 mL water (at a rate of 200 mL over 1 hour), until pH >7.0.

   b. If arterial pH <6.9, give $NaHCO_3$ 100 meq + KCl 20-30 meq in 400 mL water (at a rate of 400 mL over 2 hours), until pH >7.0.

8. Phosphate is also replaced IV if the serum level is <1 mg/dL, since severe hypophosphataemia can also lead to myocardial dysfunction and muscle weakness. It is given as K_3PO_4 20-30 mmol over 24 hours, while monitoring serum calcium levels (watch out for hypocalcaemia).

9. During treatment some patients develop increased intra-cranial pressure (ICP).Several mechanisms have been postulated for this:

   a. The increase in ICF osmoles (as a compensatory mechanism, explained above) 'backfires' when the ECF hypertonicity is corrected rapidly by treatment. The cells will need some time to readjust to the falling ECF tonicity, and if this fall happens too fast, the ICF will now become hypertonic in relation to the ECF. This will cause osmosis of water into the cell with resultant cellular oedema. Since the brain is encased within the rigid skull, this will result in increased ICP.

b. The rapid correction of hypovolaemia leads to rapid restoration of brain reperfusion, and this leads to expansion of its ECF and cerebral oedema (this has been observed on MRI scans), possibly because the cerebral circulation needs some time to recover its autoregulation.

Whatever the mechanism, it is apparent that over-rapid correction of the fluid deficit is possibly responsible for this increase in ICP, and since this can be life-threatening (by causing tonsillar herniation at the foramen magnum), it is important to 'slow down' fluid replacement once the dehydration itself is no longer life-threatening.

***Points to ponder*:**

1. *What is anion gap?*

2. *How does intra-venous $NaHCO_3$ cause intra-cellular acidosis?*

3. *The DKA patient suffers from hypoxia, due to a combination of hypoxic hypoxia (if there is concurrent pathology in gas exchange in the lung) and stagnant hypoxia (due to severe dehydration). How will the administration of intra-venous $NaHCO_3$ affect hypoxia at tissue level?*

Further reading:

Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. In Van den Berghe G (guest editor): *Endocrinology and Metabolism Clinic of North America: Acute Endocrinology* 2006; 35(4): 725-52.