Diabetic Ketoacidosis in Adults: Part 1. Pathogenesis and Diagnosis

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ABSTRACT

The metabolic derangements that lead to Diabetic Ketoacidosis (DKA) are described. Understanding the pathogenesis is the key to rapid and accurate diagnosis and hence successful management. DKA may often be prevented by clear advice to patients about how to manage their type 1 or ketosis-prone type 2 diabetes during periods of intercurrent illness. DKA must be considered in the differential diagnosis of metabolic acidosis even where other diseases that may present similarly, such as malaria, are highly prevalent.

Key words: Diabetic ketoacidosis, pathogenesis, diagnosis, emergency, prevention.

INTRODUCTION

Diabetic Ketoacidosis (DKA) is a life-threatening medical emergency characterized by high anion gap metabolic acidosis, hyperglycaemia, ketone accumulation and volume depletion. Although traditionally considered a complication of type 1 diabetes, DKA is now also commonly encountered as a complication of 'ketosis-prone' type 2 diabetes. Diagnosis may be delayed, particularly in those presenting with a new diagnosis of diabetes, as its presentation closely mimics other medical emergencies caused by a range of conditions such as infectious diseases or the 'acute abdomen' (e.g. appendicitis, diverticulitis, bowel perforation).[1] Although mortality rates have fallen to <1% in some countries over the past 20 years, they have been reported to remain as high as 29% in others.[1] The presentation of malaria, common in tropical Africa and many other parts of the world, with confusion, diarrhoea and vomiting, malaise, metabolic acidosis and renal impairment closely mimics the presentation of DKA and can sometimes lead to delayed diagnosis of DKA. Timely recognition of DKA is important to minimize complications and death. Many individuals with new onset diabetes, including children, remain undiagnosed until they present with DKA.[2]

This review is presented in three separate articles in the same issue of the journal. In this, the first part, we discuss the pathogenesis and diagnosis of DKA. In part two we focus on the clinical management of DKA and in part 3 we consider some of the pitfalls that may be encountered, as well as the management of DKA in some special situations, such as renal failure and pregnancy.

Management of children with DKA is beyond the scope of this article and the reader is referred to detailed published guidelines for the management of DKA in children.[3]

PATHOGENESIS OF DKA

Clear understanding of the pathogenesis of DKA is helpful in planning its management. Figure 1 summarizes this pathogenesis which is explained in detail below.

DKA develops either due to absolute insulin deficiency or to relative insulin

deficiency associated with an increase in counter-regulatory hormones (especially glucagon, catecholamines and cortisol).

During conditions of reduced insulin/glucagon ratio, hyperglycaemia exceeding the threshold for renal tubular reabsorption of glucose develops causing a brisk osmotic diuresis with water and electrolyte losses which lead to dehydration and eventually extracellular fluid volume depletion. The ensuing plasma volume contraction causes compensatory release of more counter-regulatory hormones (particularly cortisol and catecholamines) which lead to ever worsening hyperglycaemia and volume depletion in a positive feedback loop. At the same time, decreased renal plasma flow causes secondary hyperaldosteronism and additional potassium losses.

Individuals with DKA are potassium depleted, often with a total body K^+ deficit of 400 mmol or more (3–5 mmol/kg). As most K^+ ions are intracellular, and in the presence of acidosis and insulin deficiency, blood tests often give a poor estimate of the severity of the deficit and can show low, normal or even high serum [K^+] concentrations.[4] The positive feedback loops caused by volume depletion thus worsen hypokalaemia and hyperglycaemia and are important in the development of DKA.[5]

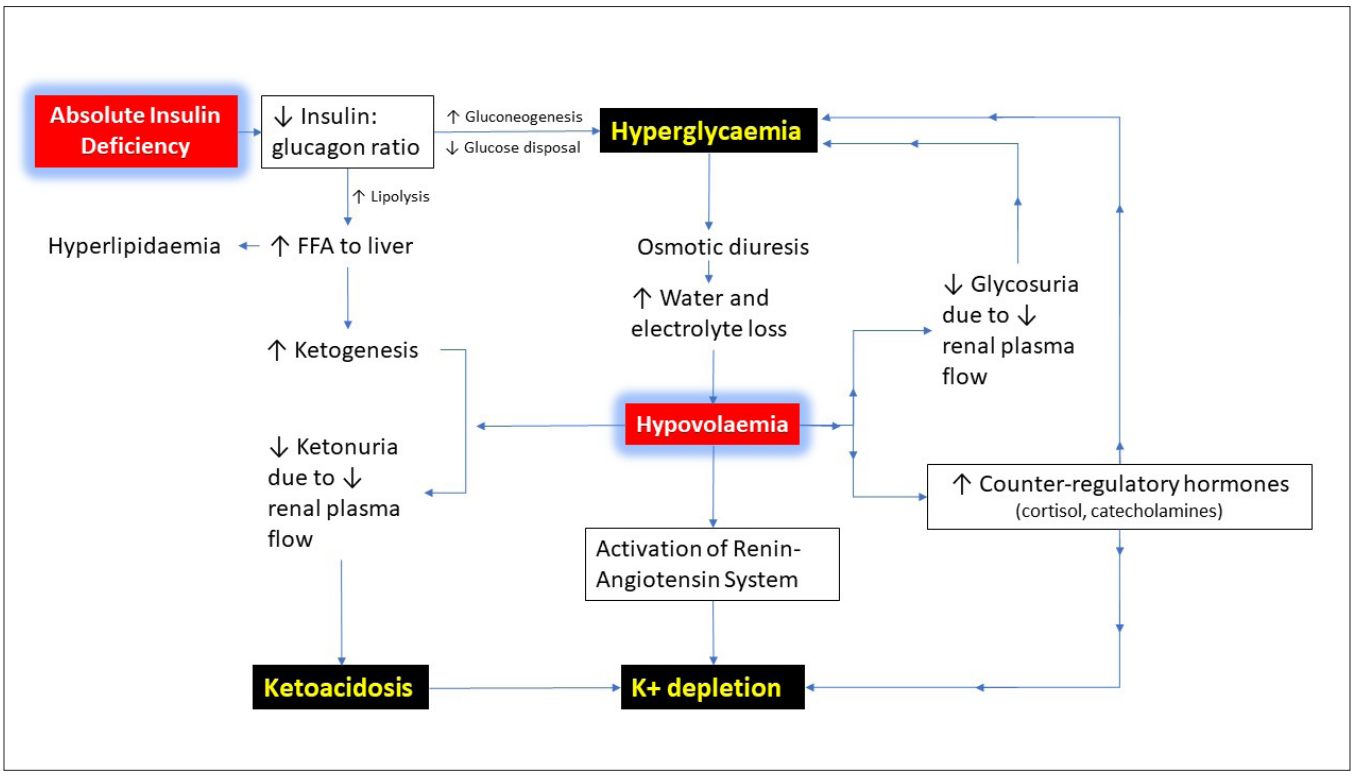
Normally, hyperglycaemia should suppress glucagon via insulin release within pancreatic islets. In DKA, glucagon levels may be markedly elevated despite profound hyperglycaemia. This occurs due to sympathetic stimulation of islet alpha cells secondary to the volume depletion that develops during DKA, and also due to severe loss of beta-cell mass (or function) that removes tonic inhibition of the alpha cell by insulin. Elevated glucagon levels increase both hyperglycaemia and ketone production.[6]

With insulin deficiency and high glucagon levels, the low insulin to glucagon ratio promotes breakdown of triglycerides through activation of hormone sensitive lipase in adipose tissue releasing free fatty acids (FFA) and glycerol. FFAs generate acetyl-CoA in the liver (through beta-oxidation) which then enter the Krebs cycle to generate ATP. As acetyl-CoA is produced in large quantities under these conditions, the capacity of the Krebs cycle becomes saturated and acetyl-CoA diverts into the ketogenic pathway resulting in the production of ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone).[7]

Hyperglycaemia, increased glucagon and increased levels of other counter-regulatory hormones such as adrenaline and cortisol all contribute to insulin resistance and decreased glucose uptake in skeletal muscles.[8]

PREVENTION OF DKA- 'SICK DAY RULES'

DKA will be slow to develop in a well hydrated individual even in the presence of significant insulin deficiency.



FFA (Free Fatty acids), Gluconeogenesis (glucose synthesis)

Figure 1. Pathogenesis of DKA (Credit: Ali Azkoul, Sing Sim and Victor Lawrence)

Attention to hydration, together with continuing insulin administration, forms the basis of the 'sick day rules' which should be explained to all patients at risk of DKA to equip them to avoid it. In the UK, the patient group 'Diabetes UK' has a website with a wealth of information (available in many languages) for both patients and medical professionals, including information on 'sick day rules', the use of which may help prevent the development of DKA in patients during an intercurrent illness https://www.diabetes.org.uk/. These guidelines are primarily designed for those who manage their diabetes with basal-bolus insulin regimes or insulin pumps. It is much more difficult to adjust insulin doses in twice daily mixed insulin regimes and no universally accepted guidance exists on this although the principles are as follows.

In general, it is vitally important, in order to avoid DKA, that people with type 1 diabetes never stop their insulin and consider 10-20% dose increases particularly if blood glucose levels exceed 10-14 mmol/l and/or in the presence of increased blood ketone levels (hydroxybutyrate >0.6 mmol/l and particularly when >1.5 mmol/l) or more than trace urine ketones. It is advisable to test blood glucose levels, and, where possible, urine or (ideally) blood ketone levels at 4-6 hourly intervals day and night during acute intercurrent illness. Testing at 2-hour intervals is recommended if blood glucose levels exceed 14 mmol/l and/or capillary blood beta-hydroxybutyrate levels exceed 1.5 mmol/l. It is important to emphasise that insulin should not be stopped even if vomiting. In this situation, carbohydrate-rich fluids should be sipped if less than about 50g carbohydrate can be taken in as food in a 4–6-hour period unless blood glucose levels are increasing or exceed 10-14 mmol/l in which case carbohydrate-free liquids should be taken instead. People with diabetes can be reassured that even if they continue to vomit, a significant proportion of the fluid and carbohydrate may still be absorbed. The principle here is to maintain the blood glucose levels high enough for normal/slightly increased insulin doses to be given safely (without inducing hypoglycaemia) in association with abundant fluid intake to prevent a spiral into DKA.

It is important for individuals with diabetes to seek urgent medical care if they cannot maintain the necessary fluid intake (ideally at least 100-200 mls/h in small regular amounts), become dehydrated or experience rising blood glucose and/or ketone levels (>1.5 mmol/l that do not reduce rapidly or >3.0 mmol/l at any time). Urgent medical care is also needed if symptoms of DKA develop (rapid breathing, abdominal pain, drowsiness, vomiting where this is not part of the intercurrent illness). Women with diabetes who are pregnant, unwell and have elevated ketones should seek urgent medical care, usually in hospital, immediately.

Certain medications should be temporarily discontinued during intercurrent illness to avoid side effects driven by any associated dehydration. These include, but are not limited to, ACE inhibitors/Angiotensin Receptor Blockers, diuretics, metformin, and non-steroidal anti-inflammatory drugs (NSAIDS). Sodium-glucose Cotransporter-2 (SGLT2) inhibitors should not generally be used in patients at risk of DKA (type 1 diabetes or ketosis-prone type 2 diabetes) and should certainly be stopped during an intercurrent illness.

Education for 'sick days' and ideally provision of ketone meters and testing strips with instructions about how and when to test (e.g. on sick days, where blood glucose levels exceed 14 mmol/l on 2 consecutive tests or if exercise is planned after one test or on any occasion that blood glucose is >18 mmol/l) should be an integral part of diabetes care.

PRECIPITATING FACTORS FOR DKA

- New diagnosis of type 1 diabetes.
- Limited adherence to agreed insulin treatment plans (e.g., because of conflicting health priorities or beliefs or lack of availability or affordability of insulin) or inadequate insulin doses (e.g., equipment failure, lack of dose titration or attempts to control weight by use of inadequate insulin doses, an increasingly recognised form of self-harm particularly where recurrent).
- Insulin denaturing due to storage at temperatures over 25-30^{0}C (depending on the specific insulin brand) or inadvertent freezing during storage close to the freezer compartment in a refrigerator. Unopened insulin should ideally be kept refrigerated at 2-8^{0}C during storage. The pen/vial in current use can generally be stored at 'room temperature' depending on the manufacturer's instructions as long as it is out of direct sunlight and assuming 'room temperature' is less than 25-30^{0}C). When damaged by heat, 'clear' insulin may become cloudy and 'cloudy' insulin may appear 'grainy' and stick to the side of the glass. Insulin that has been exposed to bright sunlight sometimes has a brownish colour. If there is a risk of heat-damage, insulin in use should also be stored in the refrigerator or in a 'cool bag' as long as it does not freeze. Insulin which may have been damaged by temperature should never be used.
- Intercurrent illness – e.g., acute coronary syndrome, acute infectious diseases, pancreatitis, cerebrovascular accident, diarrhoea and vomiting, Covid-19 infection without attention to 'sick day rules' (see 'sick day rules' above).
- Drugs – SGLT2 inhibitors, steroids, atypical antipsychotics, tocolytics in pregnancy.
- Ketosis prone type 2 diabetes (often in African/Caribbean populations).

Dehydration	→	Dry tongue, loss of skin turgor, tachycardia and hypotension
Hyperglycaemia	→	Polyuria, polydipsia, fatigue, headache, abdominal pain (impaired gastrointestinal motility)
Ketoacidosis	→	Deep breathing (Kussmaul's sign), sweet smell of mouth breath (acetone)
Hypokalaemia	→	Not usually clinically apparent unless exceptionally severe

DIAGNOSIS OF DKA

The cardinal clinical features of DKA are shown in the box above.

All of these acting together may contribute to drowsiness. Although the term 'diabetic coma' is sometimes used, true coma, as opposed to a degree of drowsiness, is very unusual and other causes should be considered where a patient in DKA presents with true coma (e.g., central nervous system infection, stroke).

The Joint British Diabetes Society for Inpatient Care (JBDS-IP) guidelines for DKA diagnosis.[9]

Reference to this excellent, freely available, and comprehensive guideline for detailed algorithms for the diagnosis and hour by hour management of DKA in adults is recommended. Unless specified to the contrary, Part 2 of these reviews[10] - giving practical management guidance- has been taken and adapted from this guideline.

All the following must be present to make the diagnosis of DKA:

1. The **'D'** – a blood glucose concentration of >11.0 mmol/L (200 mg/dL) or pre-existing diabetes mellitus
2. The **'K'** – a capillary or blood ketone concentration of >3.0 mmol/L (measures beta-hydroxybutyrate) or significant ketonuria (2+ or more on standard urine sticks which measure acetoacetate). Blood beta-hydroxybutyrate levels >6.0 mmol/l indicate 'severe' DKA.
3. The **'A'** – a bicarbonate concentration of <15.0 mmol/L and/or venous pH <7.3. Arterial blood gasses are generally un-necessary in DKA unless there is evidence of hypoxaemia.

DKA causes a high anion gap metabolic acidosis. The American Diabetes Association (ADA) recommends calculating the anion gap and this may be particularly useful if direct ketone measurement is not possible.[6] Anion Gap = $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$ Normal range 10-14.

A raised anion gap implies the presence of unmeasured anions which in this context are assumed to be ketones. This can be recalculated during treatment to assess progress if direct ketone measurement is not available.

INVESTIGATIONS

Further investigations depend on the context but may include any or all of the following tests depending on availability and degree of clinical suspicion

Blood tests:

- Venous blood gas (pH, HCO_3, electrolytes, lactate, glucose)
- Ketones (capillary/ urine as above)
- Glucose (blood and/or capillary)
- Serum urea and electrolytes
- Full Blood Count
- C-reactive protein
- Blood culture
- Amylase, cardiac enzymes etc.
- Tests for malaria/ other infections if suspected

Urine tests:

- Dipstick (ketones, signs of urinary tract infection, proteinuria etc.)
- Microscopy, Culture and Sensitivity.
- Pregnancy test in women of child-bearing age (DKA during pregnancy carries a high risk of foetal loss, see section on DKA in Pregnancy.[11]

Other:

- Electrocardiogram (ECG).
- Chest X-ray and/or other imaging.
- Lumbar puncture if central nervous system infection is suspected.

SUMMARY

In this, the first of three articles on DKA, we have discussed the sequence of metabolic derangements that culminate in DKA. Understanding the pathogenesis is the key to rapid and accurate diagnosis as well as to successful management of this condition. Furthermore, it will be seen that DKA may often be prevented by clear advice to patients about how to manage their type 1 diabetes during periods of intercurrent illness and by sound understanding of how to break or reverse the vicious cycles that all too often culminate in DKA.

We stress that DKA should be considered in the differential diagnosis of metabolic acidosis even in settings where other diseases that may present somewhat similarly, such as malaria, may much more commonly be encountered.

In part 2 of this review, we will discuss the management of DKA based on the Joint British Diabetes Society for Inpatient Care (JBDS-IP) guidelines for DKA.[9]

By these means, we hope that the goal of significantly reducing mortality from DKA, which is almost uniformly lethal if not recognised early and treated appropriately, may be realised.

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