Emergencies in diabetes — diabetic ketoacidosis and hyperosmolar hyperglycaemic state

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Abstract

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are life-threatening emergencies in diabetes mellitus. Prompt clinical suspicion and confirmation of these diagnoses is vitally important. Protocol-based treatment, involving intravenous fluids and electrolyte replacement in both cases, with intravenous insulin used in DKA (but not always in HHS) and close monitoring, can then be started to reduce associated morbidity and mortality. Every effort should be made to identify the cause so that future preventive measures can be taken. Review by a diabetes team can ensure that diabetes treatment regimens are appropriate, educational updates are provided and patient follow-up is arranged to reduce the risk of recurrence.

Keywords Diabetes; diabetic ketoacidosis; hyperosmolar hyperglycaemic state; MRCP

Key points

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are life-threatening emergencies in diabetes mellitus
- They arise from an absolute or relative insulin deficiency when a precipitant (e.g. sepsis) causes significant hyperglycaemia, aggravated by a rise in serum counter-regulatory hormones
- Prompt clinical recognition is key to support the prompt commencement of protocol-based treatment, with close monitoring to reduce morbidity
- A cause of DKA or HHS should always be sought
- Patient review by a diabetes team can ensure that diabetes treatment regimens are appropriate and educational resources are offered to reduce the risk of recurrence of these emergencies

Definitions

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are medical emergencies in type 1 and type 2 diabetes mellitus. DKA is defined as a triad of hyperglycaemia (or history of diabetes), ketonaemia and metabolic acidosis. It should be noted that euglycaemic DKA, with normal blood glucose concentrations, can occur in pregnancy and in people using sodium glucose co-transporter 2 (SGLT2) inhibitor tablets ('flozins' — which reduce blood glucose by causing controlled glycosuria) as part of their diabetes treatment.

HHS is defined by severe hyperglycaemia, high serum osmolality and dehydration. Although these are often described as separate emergencies, their presentations can overlap. UK diagnostic criteria for DKA and HHS are summarized in Table 1.

Pathogenesis

It is vitally important to remember that insulin is essential for survival — it promotes the cellular uptake of glucose for use as an energy source, reduces hepatic glucose output and promotes muscle and fat deposition. HHS and DKA develop as a consequence of relative or absolute insulin deficiency, respectively, further compounded by an increase in circulating counter-regulatory hormones.

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With DKA, in response to a stressor, this rise in counter-regulatory hormones drives further gluconeogenesis and glycogenolysis. This results in worsening hyperglycaemia in the face of insulin deficiency, meaning that cells cannot take up glucose. As a result, *absolute* insulin depletion prompts the activation of hormone-sensitive lipase in adipose tissue, which promotes fat breakdown for use as an alternative fuel source. The resulting fatty acid oxidation produces ketoacids as a toxic by-product. Hyperglycaemia and hyperketonaemia cause an osmotic diuresis, resulting in hypovolaemia, and in electrolyte imbalance from the urinary loss of key ions such as sodium, potassium and chloride.

For HHS, the *relative* insulin deficiency is associated with a more significant osmotic diuresis, resulting in more severe dehydration than in DKA, usually without significant hyperketonaemia.

Causes of DKA and HHS

Situations that can predispose to DKA or HHS are shown in Table 2.

It is worth mentioning that someone with known type 1 diabetes is at increased risk of developing DKA as an inpatient in a UK hospital.[2] This is often attributed to healthcare professionals either not prescribing or administering insulin appropriately, without fully appreciating the consequence of missed or delayed insulin in type 1 diabetes mellitus. Vigilance is needed.

The risk of SGLT2-inhibitor-associated euglycaemic DKA is particularly increased if the use of this medication class is associated with recent surgery, acute illness, insulin withdrawal or reduction, dehydration or alcohol excess.

Clinical assessment of a patient with suspected DKA

DKA can affect both young and old individuals, so patient age at presentation is less relevant. DKA typically develops over hours to days. Although some patients seek medical advice if they detect

Diagnostic criteria for DKA and HHS

DKA — all 3 of

- Plasma glucose concentration >11.1 mmol/litre or a previous history of diabetes mellitus
- Plasma ketones of ≥3 mmol/litre (urine ketones can be misleading and unhelpful)
- A pH of <7.3, an anion gap >12 or a bicarbonate concentration <18 mmol/litre

HHS — characteristic features

- Plasma glucose concentration >30 mmol/litre
- pH >7.3
- Serum bicarbonate concentration >15 mmol/litre
- Plasma ketones <3 mmol/litre
- Serum osmolality[a] >320 mOsmol/kg

Adapted from Joint British Diabetes Societies for Inpatient Care (2020).[1]
[a] Serum osmolality = $2[Na^+]$ + glucose + urea.

Table 1

Situations that can predispose to DKA or HHS

Causes of DKA

- New presentation of type 1 diabetes
- Sepsis
- Intercurrent illness
- Alcohol excess/substance abuse
- Surgical cause
- Inadequate insulin dosing or omission
- 'Mechanical' factors — e.g. broken insulin pen, problem with personal insulin infusion pump or insulin delivery technique, expired insulin
- 'Human factors' — insulin erroneously withheld in hospital patients with type 1 diabetes
- SGLT2 inhibitor therapy
- Reduced carbohydrate intake (e.g. <50 g/day resulting in fat being preferentially metabolized for energy)

Causes of HHS

- New presentation of type 2 diabetes
- Medications: high-dose corticosteroids, atypical antipsychotics
- Alcohol excess
- Sepsis
- Cerebrovascular disease
- Trauma
- Long lie
- Reduced fluid intake (e.g. reduced thirst in older age)
- Reduced fluid access

Table 2

hyperglycaemia or raised ketones on their own monitoring devices, this is not always the case. Common presenting symptoms with the associated underlying pathophysiological causes and signs are shown in Table 3. It must be remembered that these clinical features are non-specific, so clinical vigilance is needed.

The importance of the 'ABCDE' assessment of acute patients cannot be understated. Clinicians should recognize that rapid, deep *breathing* may not just reflect a primary respiratory problem but could actually be a physiological response to significant metabolic acidosis as the patient attempts to blow off acidic carbon dioxide to raise the blood pH. Similarly, *disability* could be the result of a reduced conscious level caused by significant hyperglycaemia (blood glucose >30 mmol/litre). Appropriate *exposure* of the patient is also critical, with any bandages or dressings removed, as this could reveal a source of sepsis, such as an infected foot ulcer.

Clinical assessment of a patient with suspected HHS

Although HHS usually affects older patients, both the use of high-dose corticosteroids and the increased prevalence of type 2 diabetes mellitus in younger adults can increase the risk in this group. HHS usually develops over several to many days, with patients commonly presenting severely dehydrated in a drowsy

Clinical features of DKA

Symptoms

- Unplanned weight loss (fat breakdown) — usually new type 1 diabetes
- Polyuria, polydipsia (osmotic diuresis caused by hyperglycaemia)
- Nausea and vomiting (hyperketonaemia)
- Abdominal pain (acidosis-induced ileus)
- Lethargy (cells lacking glucose as a metabolic substrate)
- Shortness of breath (breathing harder to correct an acidotic state by expelling carbon dioxide)

Signs

- Tachypnoea (Kussmaul breathing — deep and laboured)
- Dehydration ± postural drop in blood pressure
- Fruity smell on breath
- Tachycardia

Table 3

or stuporous state. A collateral history is often needed to help clinicians in their assessment.

Investigations in suspected DKA or HHS

The diagnosis of DKA or HHS should be made promptly to enable treatment to be started and to reduce the risk of morbidity and mortality. Initial measurements of blood glucose, ketones, osmolality and acid–base status should be performed early, in addition to other usual baseline investigations, such as renal function and full blood count. A septic screen should be performed (e.g. chest X-ray, blood cultures), as well as a pregnancy test, as guided by the clinical picture. Significant hypo- or hyperkalaemia should prompt electrocardiography, with associated cardiac monitoring.

Confirming the diagnosis of DKA or HHS

The criteria for either DKA or HHS as shown in Table 1 should be used. It is important to consider alternative causes of a raised anion gap metabolic acidosis, such as methanol, ethylene glycol or excessive salicylate ingestion, as these require additional treatment considerations.

Clinical management

There should be local hospital protocols for the management of DKA (adult and paediatric protocols) and HHS based on national guidance,[3,4] which should be followed when either diagnosis is confirmed. Senior or specialist review of these patients, with the involvement of other teams (e.g. critical care, obstetrics) as needed, should be part of clinical management. Clear communication with the patient and next of kin where possible can also help reduce their anxiety.

Presenting the detailed management of DKA and HHS is beyond the scope of this article; included here is an overview of the rationale for the key elements in the treatment protocols. An international Consensus report was recently published in an effort to globally standardize the management of hyperglycaemic emergencies in adults with diabetes.[5]

Management of DKA

For DKA, the key aims are as follows:

- **Restore circulating volume** – using intravenous normal saline, with additional glucose-based fluid (as a substrate for insulin) once the blood glucose concentrations approach normal, to prevent hypoglycaemia. Care must be taken with the rate of fluid replacement, particularly in young individuals (risk of cerebral oedema), in those with active cardiac, renal or hepatic problems and in pregnancy.
- **Correct electrolyte imbalance and acidosis** – through intravenous hydration and potassium replacement.
- **Correct hyperglycaemia with intravenous insulin** – usually using a weight-based infusion rate, which also suppresses further lipolysis and ketone production. Continuation of patients' usual subcutaneous long-acting (basal) insulin, at the usual dose if known, is also advised. This is so that once the patient is 'cured' of DKA, a more rapid transition from intravenous to subcutaneous insulin and a reduced length of hospital stay will be enabled as basal insulin is already 'on board'. In addition, the serum half-life of rapid-acting insulin in infusions is only a few minutes; hence were this infusion interrupted, there would be a risk of rebound ketosis that would be reduced if basal insulin was in place.
- **Use close monitoring** – to ensure metabolic parameters are improving, i.e. ketone concentrations are decreasing, blood glucose concentrations are falling (but not causing hypoglycaemia), blood pH and bicarbonate concentration are increasing, and serum potassium and fluid balance are at appropriate levels. A delayed response to treatment should prompt a check of infusion equipment or consideration of other concurrent clinical issues.
- **Identify and address the precipitant where possible** – to help reduce risk of recurrence.

Resolution of DKA typically occurs within 12–24 hours and is suggested when blood ketone concentrations are <0.6 mmol/litre and/or venous pH is >7.3. Resumption of a full subcutaneous insulin regimen should only be considered when the patient can eat and drink appropriately; otherwise intravenous insulin along with glucose-based fluids should be continued.

Management of HHS

For HHS, the key aims are as follows:

- **Restore circulating volume gradually** – initially with intravenous normal saline, potentially needing to use 0.45% normal saline if plasma glucose concentration or osmolality plateaus. As with DKA, caution with fluid replacement is advised if there are active renal, cardiac or hepatic problems. Additional glucose-based intravenous fluid can be needed once the blood glucose concentration approaches normal concentrations, to prevent hypoglycaemia.
- **Reduce plasma hyperosmolality and hyperglycaemia** – initially with fluid replacement but, unlike DKA, with concurrent intravenous insulin started only if there is hyperketonaemia (suggesting lipolysis) or blood glucose concentrations start to plateau. Close regular monitoring of plasma osmolality, glucose and electrolytes is necessary.
- **Reduce the thrombotic risk resulting from a hypercoagulable state** – by using prophylactic anticoagulation.
- **Reduce the risk of foot ulceration** – using foot protection measures and surveillance.
- **Identify and address the precipitant where possible.**

Resolution of HHS can take up to 72 hours and is influenced by patient co-morbidities and the precipitant. The patient's conscious level should be improving along with the plasma glucose concentration and osmolality. Intravenous treatment can be discontinued once the patient is able to eat and drink, and when alternative glucose-lowering therapies are started or resumed as needed.

Reducing the risk of recurrence of DKA and HHS

Every effort should be made to identify the predisposing factors. In the case of suspected mental health issues (e.g. deliberate insulin omission as self-harm, overdose, eating disorder, etc.) or alcohol-related problems, support from relevant agencies should be offered.

Patient review by the hospital diabetes team is strongly advised before the patient is discharged. This provides an

opportunity to review current diabetes control and treatment regimens (e.g. continuing use of SGLT2 inhibitors), provide additional monitoring equipment if needed and check knowledge of 'sick day rules' (e.g. to *never* stop basal insulin with type 1 diabetes, suspend SGLT2 inhibitors when unwell, etc). Educational materials and care plans can also be provided for families and carers, with specialist follow-up arranged if needed. All these measures can reduce the risk of recurrence and need for readmission. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 45-year-old woman presented with a 3-day history of vomiting and abdominal pain. She had a history of alcohol dependency and type 2 diabetes mellitus, treated with metformin and dapagliflozin.

Investigations

- Plasma glucose 12 mmol/litre (3.0–6.0)
- Serum ketones 3.8 mmol/litre (≤0.6)
- Venous pH 7.25 (7.31–7.41)

What is the most likely diagnosis?

A. Lactic acidosis associated with metformin use
B. Hyperosmolar hyperglycaemic state
C. Alcoholic ketoacidosis
D. Euglycaemic diabetic ketoacidosis
E. Starvation ketoacidosis

Question 2

A 20-year-old man presented with increased drowsiness and confusion a few days after starting regular high-dose dexamethasone for an intracranial mass effect caused by a primary brain tumour. He had no other significant history. Apart from drowsiness, clinical examination was non-contributory.

What is the next most appropriate step in clinical management?

A. Start an intravenous insulin infusion
B. Seek a neurosurgical opinion
C. Measure the plasma glucose and osmolality
D. Administer glucose intravenously
E. Measure plasma ketones

Question 3

A 25-year-old man presented as an emergency with progressively increasing shortness of breath over several hours. He had a history of anxiety disorder, had a 5 pack–year smoking history and was following a low-carbohydrate diet to lose weight.

On clinical examination, he appeared anxious, with a heart rate of 120 beats/minute, and respiratory rate 35 breaths/minute. The chest was clinically clear.

He was given oxygen and several nebulized bronchodilators, but without improvement.

Investigations

- Arterial blood gas results (on room air, before starting oxygen):
  - pH 7.2 (7.35–7.45)
  - PO_2 12 kPa (11.3–12.6)
  - PCO_2 3.5 kPa (4.7–6.0)
  - Bicarbonate 10 mEq/litre (21–29)
- Plasma lactate 5 mmol/litre (0.6–1.8)
- Plasma glucose 11.2 mmol/litre (3.0–6.0)

What is the most likely diagnosis?

A. Lactic acidosis
B. Hyperventilation syndrome
C. Acute asthma exacerbation
D. Diabetic ketoacidosis
E. Starvation ketoacidosis