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Chapter Editor
Robert Semple PhD FRCP
Wellcome Trust Senior Research Fellow and
Honorary Consultant Physician,
University of Cambridge Metabolic Research
Laboratories, UK

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Diabetic ketoacidosis and hyperosmolar crisis in adults

Ketan Dhatariya

Abstract

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) remain two of the most commonly encountered metabolic emergencies. They are both potentially life threatening when not managed correctly. DKA occurs most frequently (but not exclusively) in people with type 1 diabetes who are absolutely insulin deficient. HHS (formerly known as HONK – hyperosmolar non-ketotic state) occurs most frequently (but not exclusively) in more elderly people with type 2 diabetes, who have insufficient insulin concentration to lower blood glucose but enough to prevent ketone production. Diabetes may present for the first time as DKA or HHS, but these conditions occur more frequently in people known to have diabetes. The treatment of DKA and HHS differs because the conditions are biochemically different. In DKA the emphasis of treatment has changed; with increasing access to bedside plasma ketone monitors, β -hydroxybutyrate concentration rather than blood glucose is often used to guide therapy. In HHS, glucose lowering should be achieved predominantly using fluid rehydration, with insulin being introduced only when the rate of glucose lowering has stabilized.

Keywords Diabetes; diabetic ketoacidosis; hyperosmolar hyperglycaemic state; metabolic emergency; treatment

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are acute severe metabolic complications of uncontrolled diabetes mellitus.¹ They are potentially life threatening and require swift recognition and treatment. While they may each be seen in 'pure' form, features of the two disorders may also co-exist. Increasing rigour has been applied to treatment recommendations for both conditions over the last 5 years.

Diabetic ketoacidosis

Definition and pathophysiology

Diabetic ketoacidosis (DKA) is defined by acidosis (serum bicarbonate <15.0 mmol/L and/or venous pH <7.3), ketosis (ketonaemia >3.0 mmol/L or $>2+$ ketonuria on standard urine sticks), and hyperglycaemia (blood glucose >11.0 mmol/L or known diabetes mellitus). DKA usually occurs as a consequence of absolute or relative insulin deficiency, accompanied by an

increase in counterregulatory hormone secretion. This leads to unrestrained hydrolysis of triglycerides in adipose tissue, increasing delivery to the liver of free fatty acid, which serves as ketogenic substrate; ketones include β -hydroxybutyrate, acetoacetate, and acetone, β -hydroxybutyrate being predominant in DKA. Concurrently inappropriate hepatic gluconeogenesis and glycogenolysis result in hyperglycaemia that may be severe. Figure 1 shows the pathways involved in the development of DKA, and how it differs from HHS.

Dehydration is a cardinal feature of DKA, resulting initially from osmotic diuresis due to hyperglycaemia, later exacerbated by vomiting, and eventually from inability to take in fluid due to impaired consciousness. A clinical threat is also posed by hyperkalaemia, which occurs at presentation – a consequence of acidosis and loss of insulin-driven uptake of potassium into cells – and hypokalaemia, which commonly occurs during rehydration and insulin treatment.

Morbidity and mortality

Mortality rates have fallen significantly in the last 20 years from 7.96% to 0.67%.^{2,3} It is likely that close monitoring of fluid and electrolyte status has driven this fall. The main causes of mortality in the adult population include severe hypokalaemia, adult respiratory distress syndrome, and comorbidities such as pneumonia, acute myocardial infarction and sepsis.⁴ In children and adolescents, who are not considered further in this chapter, the most common cause of mortality remains cerebral oedema.

Management of DKA⁵

The principles of managing DKA centre on:

- replenishing the fluid deficit, which serves to reduce counterregulatory hormones as well as enhancing organ perfusion
- delivering adequate insulin to suppress ketone production and lipolysis
- identifying and treating precipitants and
- restoring euvolaemia and a normal pH without inducing iatrogenic hypokalaemia.

With technological advances in recent years, how treatment is delivered and monitored has evolved in several ways. Thus, measurement of blood ketones, venous (rather than arterial) pH and serum bicarbonate are recommended as key treatment markers, with ketones and glucose measured using bedside meters when available and operating within their quality assurance range. Electrolytes are commonly analysed on near-patient blood gas analysers with only intermittent laboratory confirmation. Widely used variable rate or 'sliding scale' insulin infusions have been replaced by weight-based fixed rate intravenous insulin infusion (FRIII), starting at 0.1 units/kg/h, and long-acting basal human or analogue insulin is either continued in patients already taking them, or started at a dose of 0.25 units/kg subcutaneously once daily in those for whom DKA is the first presentation of type 1 diabetes. Resolution of DKA is defined as a venous pH >7.3 , serum bicarbonate >15.0 mmol/L, and blood ketone <0.6 mmol/L (rather than the previously recommended 0.3).

Initial assessment focuses on resuscitation, determining the severity of fluid deficit and acidosis, and a search for likely precipitants such as sepsis or myocardial infarction. The

Ketan Dhatariya MBBS MSc MD MS FRCP is Consultant in Diabetes, Endocrinology and General Medicine, Elsie Bertram Diabetes Centre Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK. Competing interests: Dr Dhatariya is the lead author on the Joint British Diabetes Societies (JBDS) Guidelines on the Management of Diabetic Ketoacidosis in Adults and one of the lead authors on the JBDS guideline on the management of the Hyperosmolar Hyperglycaemic State. He has received travel expenses and honoraria for speaking about these, and other JBDS guidelines he has co-authored.

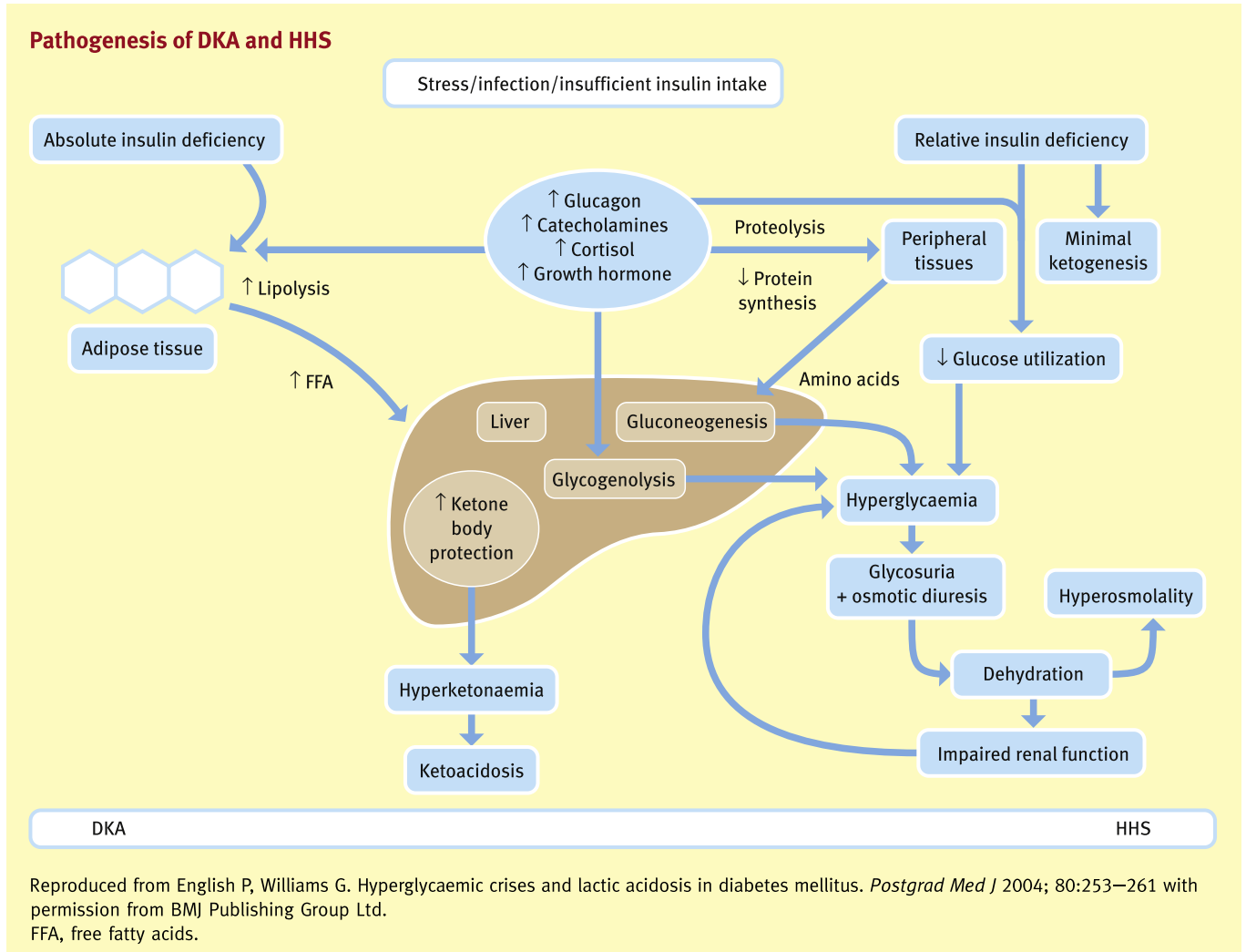


Figure 1

presence of any of the following on admission to hospital indicate admission to a Level 2/HDU environment:

- severe ketoacidosis (blood ketones >6 mmol/L; serum bicarbonate <5 mmol/L; venous or arterial pH <7.1; anion gap >16)
- hypokalaemia (<3.5 mmol/L)
- impaired consciousness (e.g. abnormal Glasgow coma score (GCS) or AVPU (Alert, Voice, Pain, Unresponsive) score)
- oxygen saturation <92% breathing air (if baseline respiratory function normal)
- haemodynamic compromise (systolic BP <90 mmHg and/or heart rate >100 or <60 beats per minute).

If systolic BP is >90 mmHg, vigorous fluid replacement should be commenced, using a regimen such as that illustrated in Table 1. Insulin should be delivered intravenously using a weight-based, fixed rate infusion (FRII). The FRIII should use an infusion pump with human soluble insulin 50 units made up to 50 ml with sodium chloride 0.9% solution. It should be infused at an initial rate of 0.1 unit/kg/h. If the patient's exact weight is not known, it can be estimated. If the patient is pregnant her present weight should be used and senior advice sought urgently. A

Typical fluid replacement regimen for DKA if systolic BP is >90 mmHg⁵

Fluid	Volume
Sodium chloride 0.9% 1 L	1000 ml over 1st hour
Sodium chloride 0.9% 1 L with potassium chloride	1000 ml over next 2 h
Sodium chloride 0.9% 1 L with potassium chloride	1000 ml over next 2 h
Sodium chloride 0.9% 1 L with potassium chloride	1000 ml over next 2 h
Sodium chloride 0.9% 1 L with potassium chloride	1000 ml over next 4 h
Sodium chloride 0.9% 1 L with potassium chloride	1000 ml over next 4 h

Re-assessment of cardiovascular status at 12 h is mandatory, further fluid may be required.

Table 1

Recommended potassium replacement regimen in DKA⁵

Serum potassium in first 24 h (mmol/L)	Potassium concentration in infusion solution (mmol/L)
>5.5	0
3.5–5.5	40
<3.5	>40 (requires senior clinical review)

Table 2

bolus dose of insulin should be used only if there is a delay in setting up an FRIII. If the patient normally takes a long-acting basal insulin (human or analogue) subcutaneously this should be continued at the usual dose and usual time to reduce the problem of rebound hyperglycaemia after withdrawal of intravenous infusion.⁶

At presentation of DKA, hyperkalaemia is common and, if severe, should be treated as an emergency. However, high serum potassium masks a deficiency of intracellular potassium in DKA, and as potassium is driven into cells by treatment with insulin and fluids serum potassium may fall sharply; it should be replaced proactively to avoid dangerous hypokalaemia. Serum potassium should be checked regularly, ideally using a near-patient venous blood gas machine. A typical replacement regimen is shown in Table 2.

Regular clinical and biochemical assessment in the hours following admission are mandatory to ensure continued improvement after initial therapy. Recommended rates of change of blood ketones, bicarbonate and glucose are shown in Table 3. Detailed management of DKA beyond 60 minutes is described in the UK national guidelines,⁵ freely available at <http://www.diabetologistsabcd.org.uk/JBDS/JBDS.htm>.

It is crucial to longer-term management, and to pre-empt future admissions, that the diabetes specialist team be involved as soon as possible after admission.

Hyperosmolar hyperglycaemic state (HHS)**Definition and pathophysiology**

HHS is a condition characterized by severe dehydration, hyperglycaemia in the absence of ketoacidosis, and hyperosmolality. Diagnostic criteria recently adopted in the UK require the presence of hypovolaemia and severe hyperglycaemia (>30 mmol/L) with serum osmolality usually >320 mOsm/kg and the absence of significant ketonaemia. HHS is believed to result from the presence of sufficient insulin to suppress hepatic ketone production, but not to suppress blood glucose.⁷ The ensuing hyperglycaemia leads to osmotic diuresis, which itself leads to dehydration and haemoconcentration, and a vicious cycle begins. The pathophysiology of HHS is illustrated in Figure 1.

HHS usually presents in elderly patients, but because type 2 diabetes is being diagnosed in ever-younger adults and teenagers, it is increasingly likely that HHS will present in younger age groups as well. Unlike DKA, which usually evolves over a matter of hours, HHS evolves over many days, and consequently the dehydration and metabolic disturbances are more extreme. However, a mixed picture of HHS and DKA may occur and may be a trap for the unwary.

Recommended metabolic targets in the management of DKA

- Reduction of blood ketone concentration by 0.5 mmol/L/h
- Increase in venous bicarbonate concentration by 3 mmol/L/h
- Reduction of capillary blood glucose by 3 mmol/L/h
- Maintenance of serum potassium between 4.5 and 5.5 mmol/L

Table 3

Hyperglycaemia induces osmotic diuresis and renal losses of water in excess of sodium and potassium. Fluid losses are estimated to be severe, at between 100 and 220 ml/kg. Despite this, the typical patient with HHS may not look as dehydrated as they are, because of redistribution of body water due to blood hypertonicity and preservation of intravascular volume.

Morbidity and mortality

Because patients with HHS tend to be older than those with DKA, they often have other comorbidities and are thus at greater risk of developing the complications not only of diabetes but also of its treatment; atherosclerosis, thrombosis, and foot ulceration pose particular risks. The reported mortality of HHS is substantially higher than that of DKA.

Management of HHS⁸

Clinical assessment should determine the extent of dehydration, evaluate mental state, and look for evidence of sepsis, a vascular event or a recent change in medication. Risk of foot ulceration should also be assessed, with obtunded or uncooperative patients assumed to be at high risk.

Investigations should delineate the biochemical severity of hyperglycaemia and acidosis, and should include calculation of osmolality (e.g. $2\text{Na}^+ + \text{glucose} + \text{urea}$). End-organ damage, in particular acute kidney injury, should be sought, as should evidence of any precipitating causes, such as inflammation, sepsis or myocardial infarction.

Immediate aims of management are to:

- replace approximately 50% of the estimated fluid loss within the first 12 hours and the remainder in the following 12 hours – the rate determined by the initial severity, degree of renal impairment and associated comorbidities
- achieve a target blood glucose of 10–15 mmol/L
- treat the underlying cause and
- prevent complications such as arterial or venous thrombosis, cerebral oedema, central pontine myelinolysis and foot ulceration.

Complete normalization of electrolytes and osmolality may take up to 72 hours. The presence of any of the following on admission to hospital indicate admission to a Level 2/HDU environment:

- serum osmolality >350 mOsm/kg and/or serum sodium >160 mmol/L
- venous/arterial pH <7.1
- severely deranged serum potassium (<3.5 mmol/L or >6.0 mmol/L)
- impaired consciousness (e.g. GCS <12 or abnormal AVPU score)

- oxygen saturation <92% breathing air (if baseline respiratory function normal)
- haemodynamic compromise (systolic BP <90 mmHg and/or heart rate >100 or <60 beats per minute)
- hypothermia
- acute or serious comorbidity (e.g. MI, CCF or CVA)
- urine output <0.5 ml/kg/h or other evidence of acute kidney injury.

If there is a problem with intravenous access, critical care support should be requested immediately. Fluid resuscitation should be guided by clinical state and comorbidity, but often starts with of sodium chloride 0.9% 1 L over 1 hour. A urinary catheter to monitor hourly urine output and calculate fluid balance is usually of value. A monitoring regimen appropriate to the patient should be established – generally hourly determination of blood glucose, serum sodium, potassium and urea, and calculated osmolality for the first 6 hours, then 2-hourly osmolality if the response is satisfactory (ideally 3–8 mOsm/L). Fluid replacement alone will lower blood glucose, which will reduce osmolality, causing a shift of free water into the intracellular space. This inevitably results in a rise in serum sodium.

Significant ketonaemia (β -hydroxybutyrate >1 mmol/L) indicates relative hypoinsulinaemia and insulin should be started at once. If significant ketonaemia is not present (β -hydroxybutyrate <1 mmol/L) insulin is not indicated. Fluid replacement alone with sodium chloride 0.9% will reduce blood glucose and, because most patients with HHS are insulin sensitive, there is a risk of lowering osmolality dangerously quickly, resulting in central pontine myelinolysis. Insulin treatment before adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with attendant decline in intravascular volume. A fall of blood glucose at a rate of up to 5 mmol/L/h is ideal; once blood glucose has ceased to fall following initial fluid resuscitation, fluid intake and renal function should be reassessed. Insulin may be started at this point using an FRIII given at 0.05 units/kg/h.

Potassium should be replaced as in DKA. An initial rise in serum sodium concentration must be interpreted in the context of what is happening to the osmolality. Provided plasma glucose is declining at a safe rate, this will be accompanied by a rise in serum sodium, but a fall in osmolality. Serum sodium concentrations should be monitored frequently, and the concentration of sodium in infusion fluids adjusted to promote a gradual decline in corrected serum sodium. Although there are no data to

indicate an optimal rate of decline in serum sodium, a rate of 0.5 mmol/L per hour has been recommended for hypernatraemic dehydration.⁹

Because of the increased risk of arterial and venous thromboembolism, all patients should receive prophylactic low-molecular-weight heparin for the duration of admission unless contraindicated. Full treatment dose anticoagulation should be considered only in patients with suspected thrombosis or acute coronary syndrome. Heel protectors should be applied in those with neuropathy, peripheral vascular disease or lower limb deformity, and feet should be re-examined daily.

Longer-term management of HHS is discussed in the recently developed UK national guidelines which are freely available.⁸ ♦

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