Hyperglycaemic hyperosmolar state

The hyperglycaemic hyperosmolar state is a diabetic emergency and its diagnosis and management differs from that of diabetic ketoacidosis. Typically a condition which affects the elderly, especially those who are frail and with multiple comorbidities, hyperglycaemic hyperosmolar state is becoming increasingly common in younger adults and can be a first presentation of type 2 diabetes. Its mortality is four times higher than that of diabetic ketoacidosis. It may be complicated by myocardial infarction, stroke, venous thromboembolism, seizures, cerebral oedema, central pontine myelinolysis and death. Indeed, it carries a mortality rate of 15–20% whereas in diabetic ketoacidosis, the mortality is less than 5%. The main causes of death in hyperglycaemic hyperosmolar state are aspiration pneumonia, cerebral oedema, thromboembolic complications or from the underlying pathology which triggered the hyperglycaemic hyperosmolar state (Steenkamp et al, 2013; Scott et al, 2015).

This article reviews the diagnosis and treatment of hyperglycaemic hyperosmolar state and highlights the particular challenges of the condition.

Pathogenesis

The basic underlying mechanism is a reduction in the effective action of circulating insulin combined with a rise in counter-regulatory hormones such as glucagon, cortisol, catecholamines and growth hormone. These hormonal alterations lead to increased renal and hepatic glucose generation and impaired use of glucose in peripheral tissues. This results in hyperglycaemia and changes in osmolality in the extracellular space. In hyperglycaemic hyperosmolar state, plasma insulin concentrations are inadequate to facilitate the use of the high level of glucose by insulin-sensitive tissues but high enough to prevent lipolysis and ketogenesis. Hyperglycaemic hyperosmolar state is also associated with glycosuria which leads to osmotic diuresis with renal loss of water to a greater degree than the loss of sodium and potassium (Kitabchi et al, 2009; Steenkamp et al, 2013; Pasquel and Umpierrez, 2014).

Severe dehydration will be further promoted in hyperglycaemic hyperosmolar state by restricted access to water. This is partly because affected patients frequently are or become unwell and bedridden and are therefore unable to access water themselves. The elderly also have an altered thirst response as part of the physiology of ageing and are therefore less likely to increase their oral intake. If they are residents of an institution (such as a care home) or dependent on others for nutrition and hydration, they may not receive increased oral fluids which are what they need once they are developing hyperglycaemic hyperosmolar state (Chau and Edelman, 2013).

Diagnosis

The characteristic features of hyperglycaemic hyperosmolar state are high osmolality (>320 mosmol/kg), high blood glucose levels (>30 mmol/litre) and hypovolaemia. There usually is no significant ketosis (less than 3 mmol/litre) but it can be accompanied by a mild metabolic acidosis (pH>7.3, bicarbonate >15 mmol/litre). Generally, it is a condition affecting older patients but it can also occur in younger adults and could even be a first presentation of type 2 diabetes (Scott et al, 2015). However, there can be cases which are a mixed picture of hyperglycaemic hyperosmolar state and diabetic ketoacidosis (severe hypotonicity, ketosis and acidosis).

The process of hyperglycaemic hyperosmolar state usually develops over days to weeks. There may be symptoms of poorly controlled diabetes such as polyuria, polydipsia and weight loss. As the patient becomes more unwell, this can progress to vomiting, dehydration, weakness, confusion, seizures and coma. While there tends to be a change in cognitive function, this can range from mild confusion to delirium or lethargy and coma. Patients with altered levels of consciousness may also have asymmetrical findings on neurological examinations and may require neuroimaging. It is also important to consider whether the airway is protected and whether the patient is at risk of retaining secretions.

Clinically, the patient may have signs of dehydration and/or signs of hypovolaemic shock (tachycardia, hypotension). However, despite severe electrolyte derangement and water depletion, the patient may not appear as dehydrated as he/she truly is, because the hypertonicity leads to movement of water from the extravascular to the intravascular space and therefore helps to preserve the intravascular volume. Assessment of fluid volume status is key to guiding patient management.

Patients with hyperglycaemic hyperosmolar state can be very unwell; they may require management on a higher dependency unit and may also require close supervision and monitoring. In this environment, patients may benefit from a central venous catheter and/or arterial line to facilitate frequent blood sampling and monitor fluid balance. It is worth noting that patients may have an increased anion gap metabolic acidosis as a result of ketoacidosis and/or raised serum lactate levels. Features that would indicate need for escalation to level 2 care are outlined in *Table 1*.

It is also important to identify the cause for hyperglycaemic hyperosmolar state when assessing the patient. The most common precipitant is infection in 40–60% of cases, with the likely sources being either the chest or the urine. Other potential triggers should be considered and include cardiac events, acute abdomen and limb

Dr Lucy-Anne Frank is ST4 in Geriatric and Internal Medicine in the Department of Elderly Care, Lister Hospital, Stevenage SG1 4AB

Dr Andrew Solomon is Consultant Physician in the Department of Endocrinology, Lister Hospital, Stevenage

Correspondence to: Dr L-A Frank (lucy-anne.frank@nhs.net)

Table 1. Features of severe hyperglycaemic hyperosmolar state

Osmolality > 350 mosmol/kg
Na+ >160 mmol/litre
pH <7.1
K+ <3.5 mmol/litre or K+ >6 mmol/litre at presentation
Glasgow Coma Scale <12
Oxygen saturation <92% (assuming normal respiratory function at baseline)
Systolic blood pressure <90 mmHg
Pulse >100 bpm or <60 pbm
Urine output <0.5 ml/kg/hour
Serum creatinine >200 micromol/litre
Hypothermia
Macrovascular event, e.g. myocardial infarction, stroke
Other serious comorbidity

Table 2. Important initial investigations

Capillary blood glucose
Venous blood glucose
Blood or urine ketones
Bloods to include full blood count, urea and electrolytes, C-reactive protein
Septic screen: chest X-ray, urine cultures, blood cultures
Arterial blood gas including lactate
Electrocardiogram
Calculate serum osmolality 2 (K+ + Na+) + glucose + urea

Figure 1. Management of hyperglycaemic hyperosmolar state.

Immediate management: 0–60 minutes

1. Assess the patient considering fluid balance, mental state, precipitating causes
2. Perform basic investigations
3. Urinary catheter and aim for 0.5 ml/kg/hr
4. Start intravenous 0.9% normal saline as 1 litre over 1 hour (without added potassium). Caution may be needed in the elderly and patients with a history of cardiac failure
5. Start intravenous insulin only if there is significant ketonaemia >1 mmol/litre or ketonuria >2+
6. Commence prophylactic low molecular weight heparin
7. Consider antibiotics
8. Establish plan for appropriate monitoring: hourly blood glucose, repeat blood tests at 6 hours and then 12-hourly, fluid balance chart

Acute management: 60 minutes to 6 hours

1. Achieve a gradual decline in osmolality (3–8 mosmol/kg/hour)
2. Aim to achieve positive fluid balance by 2–3 hours. Depending on clinical and fluid balance assessment, aim for 0.5–1 litre fluid/hour
3. Recalculate Na+, K+, renal function and osmolality
4. Adjust intravenous fluids according to plasma Na, serum osmolality and fluid balance
5. If the blood glucose is falling at less than 5 mmol/litre/hour, consider starting low dose intravenous insulin (0.05 units/kg/hour) or if already running, increase to 0.1 units/kg/hour. Avoid hypoglycaemia by keeping blood glucose between 10–15 mmol/litre in the first 24 hours. If blood glucose <14 mmol/litre, start 5 or 10% glucose in addition to ongoing fluid replacement
6. Aim to maintain potassium in the normal range by replacing as required

Subsequent inpatient management

1. Ensure that the patient is improving clinically and biochemically
2. Aim for positive fluid balance of 3–6 litres by 12 hours with intravenous fluids and continue until the patient is eating and drinking normally
3. Assess for complications of treatment (fluid overload, cerebral oedema, central pontine myelinolysis)
4. Sodium and osmolality may take up to 3 days to fully normalize
5. Convert to subcutaneous insulin when biochemically stable
6. Encourage early mobilization
7. Measure electrolytes daily
8. Remove catheter
9. Perform daily foot checks
10. Ensure that the patient has received a diabetes team review
11. Most patients should go home on subcutaneous insulin but this should be reviewed in the community

ischaemia (Kitabchi et al, 2004; Steenkamp et al, 2013). Patients may also present with foot ulceration and should have a foot examination on admission.

Important initial investigations are described in *Table 2*.

Management

The key aims of treatment in hyperglycaemic hyperosmolar state are to normalize the serum osmolality and blood glucose, replace fluid and electrolytes as necessary, prevent venous thrombosis, prevent cerebral oedema or central pontine myelinolysis, and prevent the development of foot ulceration. All of these patients should be referred to the diabetes and endocrinology team for early specialist input and be regularly reviewed by the diabetes specialist nurse. It is also crucial that the patient is cared for in an environment suited to the unwell medical patient so that he/she can receive appropriate input from the medical and nursing teams. Appropriate examples would include the acute medical unit, endocrinology ward or elderly care ward as many of the patients will be elderly, frail and with multiple comorbidities.

This section provides an outline for patient management (*Figure 1*) and covers the general principles and some controversial areas in more detail (Scott et al, 2015).

Fluids

The aim of treatment with intravenous fluids is to restore circulating volume, reverse dehydration and restore renal perfusion. The estimated fluid loss is 110–220 ml/kg. Fluid and electrolytes losses in hyperglycaemic hyperosmolar state are outlined in *Table 3*.

The recommended method of fluid replacement is with intravenous 0.9%

Table 3. Fluid and electrolyte losses in hyperglycaemic hyperosmolar state

		For 60 kg patient	For 100 kg patient
Water	100–220 ml/kg	6–13 litres	10–22 litres
Na+	5–13 mmol/kg	300–780 mmol	500–1300 mmol
Cl	5–15 mmol/kg	300–900 mmol	500–1500 mmol
K+	4–6 mmol/kg	240–360 mmol	400–600 mmol

normal saline which will replace circulating volume and correct dehydration. The aim should be to reduce the plasma sodium by a maximum of 10 mmol/24 hours and to reduce the osmolality by 3–8 mosmol/kg/hour. More rapid changes may be harmful.

All patients require assessment of their fluid status and fluids should be given according to individual patient needs. Initially, patients require fluid resuscitation and guidelines recommend considering an initial prescription of 1 litre of fluid over 1 hour (caution may be required in the frail elderly or in those with cardiac disease or known heart failure). Subsequently, 0.9% normal saline will likely need to be continued at a rate of 0.5–1 litre/hour for the first 2–3 hours but this is dependent on clinical assessment. The overall target is to achieve a positive fluid balance within the first 6–12 hours of admission to hospital. The osmolality should be recalculated and electrolytes re-measured within the first 6 hours to guide appropriate treatment. At this point:

- If the plasma Na+ is increasing but the osmolality is declining at the expected and appropriate rate, continue with 0.9% normal saline.
- If the plasma Na+ is increasing and the osmolality is also increasing, it may be necessary to increase the rate of 0.9% normal saline infusion if the fluid balance is still negative. If the fluid balance is positive, consider switching to 0.45% normal saline but senior advice should be sought before doing so.
- If the osmolality is falling too rapidly, the rate of fluid infusion needs to be reduced.

An initial rise in Na+ is expected and is not in itself an indication for switching to 0.45% normal saline, especially if the serum osmolality is declining at the expected rate. Switching to 0.45% normal saline is only recommended if the osmolality is not falling despite adequately positive fluid balance. The reason for the initial rise in Na+ is because the initial fluid replacement (even in the absence of intravenous insulin) causes a lowering of blood glucose which reduces the osmolality because this makes water shift into the intracellular space. This will inevitably result in a rise in serum Na+. A fall in blood glucose of 5.5 mmol/litre will result in approximately 2.4 mmol/litre rise in serum Na+. It is important to remember that even isotonic 0.9% normal saline is already relatively hypotonic compared to the serum in patients in hyperglycaemic hyperosmolar state, hence changing to fluids which are even more relatively hypotonic should not be done lightly and will require very close monitoring and senior support (Gouveia and Chowdhury, 2013; Scott et al, 2015).

The aim is to replace approximately 50% of lost fluid within the first 12 hours and the remainder in the next 12 hours. Whether this is achievable will be affected by the initial severity of hyperglycaemic hyperosmolar state, degree of renal impairment and balancing other comorbidities especially cardiac disease. Complete normalization of biochemistry may take several days.

As soon as it is safe to do so, patients should be encouraged to take fluids orally.

Insulin

Hyperglycaemia causes osmotic diuresis and renal losses of water in excess to the loss of sodium and potassium. Patients with hyperglycaemic hyperosmolar state are therefore dehydrated and suffer from extracellular volume depletion.

The blood glucose level should not fall by more than 5 mmol/hour. Sustained low-dose insulin infusion (0.05 units/kg/hour) will result in rapid but controlled metabolic recompensation with a reduced risk of cerebral oedema. Insulin should only be started if the blood glucose level is no longer falling with intravenous fluids alone or immediately if there is significant ketonaemia.

Intravenous insulin can be discontinued once the patient is eating and drinking again. It should then be transferred to subcutaneous insulin or oral diabetes medications (if appropriate and considering factors such as safety of administration in the community, ability to monitor the blood glucose levels, awareness of hypoglycaemia). This may only be needed for a short period of time (weeks to months) until a period of stability has been reached. At this point, switching to oral agents or reversion to previous oral treatment could be considered. These decisions should all be made after discussion with the diabetes team.

Potassium

Patients with hyperglycaemic hyperosmolar state are potassium deplete but as they are less acidotic than diabetic ketoacidosis patients, the potassium shifts are less pronounced. There is also often co-existing acute kidney injury. Potassium should be replaced as required (*Table 4*).

Antibiotics

As hyperglycaemic hyperosmolar state is triggered by infection in 40–60% of cases, if a source of sepsis is suspected or identified, antibiotic therapy should be initiated (Scott et al, 2015).

Anticoagulation

Patients with hyperglycaemic hyperosmolar state are prothrombotic partly because of hypernatraemia and raised antidiuretic hormone concentrations. Prophylactic anticoagulation is required in all patients (unless contraindicated for other reasons) (Scott et al, 2015).

Foot protection

It should be assumed that all patients are at high risk of foot and pressure area ulceration. This is especially likely if the patient is

Table 4. Potassium replacement in hyperglycaemic hyperosmolar state

Potassium level in first 24 hours	Potassium replacement in infusion solution
Over 5.5 mmol/litre	Nil
3.5–5.5 mmol/litre	40 mmol/litre
Below 3.5 mmol/litre	Senior review as additional potassium required (via central line in high dependency unit or intensive care unit setting)

uncooperative, lethargic or comatose. Patients should be on a pressure-relieving mattress, the heels need to be protected, the feet need to be checked daily and the patient turned frequently if unable to do so him-/herself (Scott et al, 2015).

Prevention

Many cases of hyperglycaemic hyperosmolar state can be prevented by better access to medical care, proper education about diabetes and the ability to effectively communicate with the relevant health-care provider in the event of worsening control or intercurrent illness. It is also worth considering screening people who are at high risk of diabetes to prevent admissions with hyperglycaemic hyperosmolar state as a new diagnosis of type 2 diabetes.

Hyperglycaemic hyperosmolar state is a condition which commonly affects the elderly, many of whom are dependent on others for care, including medications and access to food and fluids. Therefore prevention of hyperglycaemic hyperosmolar state is dependent on successful education and engagement of family and carers. Of concern, the Institute of Diabetes for Older People carried out a National Care Home Survey in 2013 which found that over a third of residents did not know about signs or symptoms of hypoglycaemia and that over a third of care home did not have a policy to manage hypoglycaemia, 17% of homes had no system in place to check medication compliance among those who took their own medications, and two thirds had no designated staff member with responsibility for diabetes management at the care home. Clearly, there is a need for better education of patients and their caregivers with regards to the management of diabetes, sick day rules, management and recognition of dehydration and diabetic complications including hypoglycaemia (Kitabchi et al, 2009; Diabetes UK, 2014; Dunning et al, 2014). **BJHM**

Conflict of interest: none.

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KEY POINTS

- Hyperglycaemic hyperosmolar state is a diabetic emergency which can present insidiously and with vague symptoms. It carries up to 20% risk of mortality and is triggered by infection in up to 60% of cases.
- Regularly measure or calculate the osmolality to monitor response to treatment.
- Aim to use 0.9% normal saline to restore circulating volume, correct dehydration and achieve biochemical normalization. The rate of fall of the plasma sodium level should not exceed 10 mmol/24 hours.
- The fall in blood glucose level should be no more than 5 mmol/hour. Low dose intravenous insulin should be commenced once the blood glucose has stopped falling with intravenous fluids alone or immediately if there is significant ketonaemia.
- Take steps to manage the risk of foot ulceration.
- Ensure that all patients receive prophylactic anticoagulation (unless contraindicated).