Anticoagulation in hyperosmolar hyperglycaemic state: a case report and review of the literature

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Introduction
Hyperosmolar hyperglycaemic state (HHS) is one of two serious metabolic derangements that occur in people with diabetes mellitus. The first cases of HHS were described by von Frerichs and Dreschfeld in the 1880s with an ‘unusual diabetic coma’. It is a serious, life-threatening, but fortunately rare emergency that, although less common than its counterpart, diabetic ketoacidosis (DKA), has around a 10 times higher mortality rate, up to 15–20%. HHS accounts for around 1% of hospital admissions in people with diabetes, typically in the elderly. Increasing prevalence of obesity has additionally increased the incidence of HHS in the paediatric population. Prognosis is worse when associated with increasing comorbidities, age and significant electrolyte abnormalities.

It is well known that diabetes can affect the clotting pathway, resulting in endothelial dysfunction, eventually enhancing the activation of procoagulant factors, predisposing towards thrombosis. This process is further amplified in both hyperosmolarity and DKA.

Several case reports highlight the significant mortality and morbidity that can be associated with venous thromboembolism (VTE) and its complications in people with hyperosmolarity including fatality from massive pulmonary embolism. Patients having major orthopaedic surgery tend to receive extended VTE prophylaxis and demonstrate significant reduction in VTE with this therapy. Given the paucity of evidence for prophylactic versus therapeutic anticoagulation in HHS, we looked at the evidence surrounding orthopaedic surgery where there has been considerable research.

Direct oral anticoagulants are now being used for VTE prophylaxis in orthopaedic patients and may have a role in acutely unwell medical patients with a low risk of bleeding.

The evidence regarding the potential benefit of prolonged anticoagulation in HHS remains unclear. We performed a literature review to look at the evidence.

Case report
Patient information
A 63-year-old man with diet-controlled type 2 diabetes mellitus for 2 years, with body mass index 28.3 kg/m², was admitted with a two-week history of lethargy and a one-month history of severe osmotic symptoms (polyuria and polydipsia). He had recently been treated for a urinary tract infection. He reported weight loss of 3 kg in the week preceding admission. Three weeks prior to presentation he had returned from the USA on a long-haul flight. He had a 24-hour history of confusion, with no associated chest pain, shortness of breath or palpitations. There was no history of alcohol consumption or smoking. There was a family history of type 2 diabetes mellitus.

Clinical findings
On admission he had a Glasgow Coma Scale of 14/15. He was tachycardic with pulse rate 100 bpm, but was otherwise hemodynamically stable although clinically dehydrated. A venous blood gas highlighted metabolic acidosis (pH 7.2), blood ketones were 3.3 mmol/L and additional laboratory investigations indicated acute renal impairment with hypernatraemia (Na⁺ 155 mmol/L, K⁺ 4.9 mmol/L, urea 39.8 mmol/L, creatinine 460 µmol/L, estimated glomerular filtration rate (eGFR) 12 mL/min and glucose 70 mmol/L, normal full blood count). His HbA₁c was 6.8% (51 mmol/mol) 6 months previously. Calculated serum osmolality was 429.6 mOsm/kg (normal range 278–305).

Diagnostic assessment
The working diagnosis on admission was a combination of HHS/DKA with infection (likely urinary tract infection) as a precipitant, acute kidney injury stage 3 and delirium presumed secondary to these conditions.

Therapeutic intervention
He was started on the trust’s HHS treatment protocol which is similar to the JBDS guidance. He was also commenced on...
prophylactic low molecular weight heparin (LMWH; dalteparin) which was accurately dosed according to weight and eGFR and stopped after 3 days as his platelet count dropped (see Table 1) after discussion with the haematology team. Although he had recently returned from a long-haul flight, the admitting team did not feel VTE was likely as he did not have clinical features suggestive of thromboembolism and had not had surgery in the previous 4 weeks. The focus was on the treatment of sepsis and HHS/DKA. He was treated with intravenous antibiotics in a dose appropriate for his renal function. His biochemical parameters, notably renal function, improved with fluid resuscitation (Table 1).

On day 2 of admission he was noted to have dynamic ECG changes with raised troponin-I (2,673 ng/L peaking at 3,820 ng/L [normal <40 ng/L]). He was initially treated for a non-ST elevation myocardial infarction. On advice of the cardiologist and the haematologist, he was started on aspirin without clopidogrel (x10^12/L), aiming for a platelet count of 149 mmol/L on the day of his CTPA. Anticoagulation treatment was challenged in view of his thrombocytopenia. He was not thrombolysed. On the advice of the haematology team he was given a platelet transfusion, aiming for a platelet count of >50x10^12/L. He was then commenced on a treatment dose of dalteparin (15,000 units) and later switched to warfarin under the guidance of the haematology team. The drop in platelet count was felt to be due to consumption coagulopathy. The plan was to give warfarin for 6 months and to be reviewed by the haematology team.

He had a coronary angiogram as an inpatient which showed unobstructed coronaries. An echocardiogram showed mild to moderate concentric left ventricular hypertrophy, no significant left ventricular outflow tract obstruction, normal systolic function and no significant valvular abnormalities. The raised troponin-I was attributed to subendocardial ischaemia in the right ventricle which is seen in acute pulmonary embolism.

### Follow-up and outcome

He was discharged home taking Humulin I insulin twice a day. When reviewed in the outpatient clinic two months later, his insulin was stopped and treatment switched to metformin alone.

### Discussion

HHS is associated with a hypercoagulable state. The onset of HHS is usually over days with significant metabolic derangements, dehydration and hyperglycaemia. This occurs due to increased levels of counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone from a relatively insulin-deficient state. Hyperglycaemia develops due to increased glycogenolysis, reduction in glucose utilisation and gluconeogenesis. In contrast to DKA, in HHS the insulin level is adequate to prevent lipolysis and ketogenesis, but not to stimulate glucose utilisation. This leads to an osmotic diuresis, resulting in intracellular dehydration and a hyperosmolar state. In HHS it can lead to significant intravascular dehydration (6–13 L in a person weighing 60 kg). There is also an increase in pro-inflammatory cytokines creating a pro-thrombotic environment. This can lead to thromboembolic events, cerebrovascular accident, disseminated intravascular coagulopathy, myocardial infarction and peripheral or central vascular occlusion. Chaudhuri and Umpierrez noted normalisation of circulating pro-inflammatory cytokines upon reduction of blood glucose concentration. The large increase in reactive oxygen species leads to damage of lipids and proteins at the cellular level.

Common precipitants include sepsis (up to 60%), poor medication adherence (21%), undiagnosed diabetes (11%) and medical illness such as stroke or myocardial infarction that causes release of counter-regulatory hormones.

### Methodology and review

We carried out a literature search using our own Clinical Information Search System (CISS) through Medline, Embase, Pubmed, Uptodate and BMJ best practice using the terms “Hypoglycaemia or HHS” in association with “DVT or PE”. We found 19 papers in total. After excluding six paediatric papers, one paper focusing on DKA and another seven papers based on their title and content, we were left with five papers describing some form of association between HHS, thromboembolism and clinical approach (Table 2 and Figure 1).

### HHS and VTE management

Diabetes alone is a risk factor for VTE in comparison with the non-diabetic population. A retrospective study of 302 adult patients (56 patients with diabetes and 246 without) identified an annual VTE incidence rate among people with diabetes of 432 per 100,000 compared with 78 per 100,000 in those without diabetes. Patients with diabetes have a 1.7-fold increased risk of VTE compared with those without diabetes. After adjusting for age, there remains a two-fold risk increase in patients with diabetes.
Table 2 Summary of articles reviewed

| Author               | Type of article | Cohort/subject                                                                 | Learning points                                                                 | Limitations                                                                 |
|----------------------|-----------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Park et al, 2006[1]  | Case report     | HHS patient complicated by extensive upper extremity venous thrombosis          | Current experiences support the safety and efficacy of catheter-directed thrombolysis. There is inadequate clinical evidence for full anticoagulation. | Case report on one patient                                                                                           |
| Hamblin et al, 1989[2] | Journal article | Hyperglycaemic complications of diabetes in people with diabetic ketoacidosis and HHS | The mortality rate was 14.6% (12 deaths) for 82 episodes of HHS. Six cases of mesenteric and iliac thromboses, eight cases of myocardial infarction and two cases of cerebral haemorrhage were identified | Therapeutic anticoagulation not given to patients prior to diagnosis of VTE                                             |
| Keenan et al, 2007[3] | Journal article | Risk of VTE in patients hospitalised for HHS                                   | 32 (1.2%) of 2,859 people with HHS developed VTE in hospital. HHS (HR=3.0) compared to DKA (HR=1.2) | Recommended extended duration of VTE prophylaxis in HHS patients, but duration unclear                               |
| Sinson et al, 2016[4] | Case report     | Renal vein thrombosis developed in an HHS patient                             | Poorly controlled type 2 diabetes is associated with high levels of plasminogen activator inhibitor-1 resulting in reduced fibrinolysis | Case report of one patient and no recommendations given for duration of VTE prophylaxis                               |
| Wordsworth et al, 2014[5] | Case report     | Massive pulmonary embolism associated with HHS                              |                                                                                     | Case report of one patient, prophylaxis anticoagulation given                                                        |

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycaemic state; HR, hazard ratio; VTE, venous thromboembolism.

![Figure 1. Methodology and review](image)

Park et al[1] reported a case of extensive venous thrombosis of the upper extremity 30 hours after placement of a subclavian venous catheter in a patient with HHS. The patient was treated with early catheter-directed thrombolysis followed by anticoagulation. Full anticoagulation was not recommended due to bleeding risk.

Hamblin et al[2] reported a mortality rate of 14.6% in 82 patients diagnosed with HHS. They identified six cases of mesenteric and iliac thromboses, eight cases of myocardial infarction and two cases of cerebral haemorrhage in these patients.

Keenan et al[3] identified an incidence of VTE in patients with HHS of 1.7%; 71% were diagnosed during hospital stay and a further 29% were diagnosed within 3 months following hospital discharge. In comparison, patients undergoing total hip replacement had a VTE incidence of around 2.8%, suggesting that patients with HHS are at very high risk of VTE. Furthermore, the incidence of VTE in those with HHS – even after adjusting for age, ethnicity, gender and recent hospitalisation – was found to be higher than that of people with uncomplicated diabetes and DKA. This work suggests that the increased thrombotic risk in patients with HHS can be attributed to the more profound hyperosmolarity and hyperglycaemia. Keenan et al have suggested extended duration of VTE prophylaxis, especially in very high-risk groups. The VTE risk is comparable to patients with sepsis and acute connective tissue disease.[3]

Sinson et al[4] reported a case of acute pyelonephritis with renal vein and inferior vena cava thrombosis. This patient was initially managed according to the HHS protocol and given prophylactic anticoagulation. Subsequently, the patient developed renal vein thrombosis and pulmonary embolism. There is an associated increase in plasminogen activator inhibitor-1 inhibiting fibrinolysis and increasing the thrombosis risk in patients with poorly controlled type 2 diabetes. Once again there were no clear recommendations for anticoagulation.

Heparin and bleeding prediction scores

It is still debatable whether all patients with HHS should be given treatment dose anticoagulation. HHS tends to occur in the older population. The risk of VTE increases significantly with age, particularly in those aged ≥75 years, with an odds ratio of 1.5 for every 10 years of increase in age. Campbell et al[5] found that ageing is associated with increased heparin levels after standard heparin doses and therefore lower heparin dose requirements. A decline in renal function, especially in patients with creatinine clearance <30 mL/min, genetic polymorphisms and drug inter-
Key messages

- HHS is a hypercoagulable state associated with significant risk of venous thromboembolism and high mortality.
- Clinicians need to assess each patient's risks independently. High risk patients with low bleeding risk should be considered for therapeutic anticoagulation throughout their hospital stay.
- Careful monitoring of the clinical status and discussion involving the haematology team if needed will help decide the optimal anticoagulation therapy.

The use of bleeding prediction scores can help guide management in patients with thromboembolic events. Klok et al reviewed the performance of the VTE-BLEED score (consisting of six objective clinical variables) and found the VTE-BLEED score to be superior to other bleeding scores in predicting bleeding risk. It is mainly used as a tool in patients with a previous diagnosis of VTE, on anticoagulation to predict bleeding risk. It also helps to guide clinicians in decision making regarding extension of anticoagulation, depending on a patient's risk of long-term VTE recurrence. They found therapeutic anticoagulation to be safe in low-risk people, but in high-risk people more studies are required. This tool is awaiting further prospective validation before being incorporated into clinical practice. It is unclear whether patients with HHS were included in this study.

With the COVID-19 pandemic there have been numerous studies looking at therapeutic anticoagulation. The ATTAC/ACTIV-4a and REMAP-CAP multipurpose randomised controlled trial suggested giving a therapeutic dose of thromboprophylaxis to hospitalised non-intensive care patients with COVID-19. The dose is weight-based unless the creatinine clearance is <30 mL/min, for which heparin assay needs to be checked on day 3. However, the evidence surrounding therapeutic anticoagulation in HHS remains limited.

A study in Canada evaluated the efficacy of extending VTE prophylaxis in acutely unwell medical patients. Using extended duration of enoxaparin reduced VTE by 1.5% but increased the variability in their INR level due to poor dietary vitamin K intake and poor absorption from altered intestinal flora.

The current JBDS guidelines recommend prophylactic LMWH for the full duration of hospital stay in people with HHS. However, there remains limited evidence on using treatment anticoagulation in people with HHS who are at high risk of thromboembolism. Most guidelines available are based on case reports and observational studies alone. Currently, an extended course of LMWH is only recommended for people at high risk. A therapeutic dose of LMWH is not currently recommended due to associated bleeding risks, unless there is evidence of acute coronary syndrome or thrombosis.

Clinicians should assess each patient's risks independently. If a person is deemed to be at high risk of thrombosis, full dose anticoagulation should be given. We have been agonising about the clinical management decision regarding anticoagulation in HHS for far too long and there is an urgent need for a randomised controlled trial.

Conflict of interest All authors have none to declare.

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