Double trouble: managing diabetic emergencies in patients with heart failure

In this paper Dr Legate Philip and Dr Ruth Poole look at the pathophysiology and epidemiology of heart failure in diabetes, heart failure drugs and their effect on diabetes; also covered are practical aspects of management of hyperglycaemic emergencies in diabetic patients with heart failure.

Introduction
Heart failure and diabetes frequently coexist and recent evidence suggests a bidirectional relationship with an increased risk of heart failure in patients with diabetes but also an increased risk of developing diabetes in patients with heart failure.1,2 Although the management of heart failure in patients with stable glycaemia is relatively straightforward, the management of the two conditions becomes difficult during diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS). Diuretics and fluid restriction are essential components of heart failure management while aggressive intravenous fluid replacement is indicated in DKA and HHS.

Epidemiology
The Framingham Heart Study3 showed that diabetic men and women were two and five times more likely, respectively, to develop heart failure compared with control subjects independent of age, hypertension, obesity, coronary artery disease and hyperlipidaemia.

Data published as early as 2001 showed that every 1% (11mmol/mol) increase in glycosylated haemoglobin (HbA1c) increased the risk of heart failure by up to 10%.4-6

In patients with chronic heart failure, the prevalence of diabetes is around 20%7-9 compared with 40% in those hospitalised with worsening heart failure.10 There is evidence that hospitalised heart failure patients with diabetes have a worse prognosis with increased rates of cardiovascular mortality and heart failure hospitalisation post-discharge compared to patients without diabetes.11,12

Pathophysiology
Diabetes is a multi-system disorder affecting many organs both at a macro- and microvasculature level. Hyperglycaemia, associated glycated proteins and dyslipidaemia damage macrovasculature leading to atherosclerosis and risk of cardiovascular disease.1,13 Diabetes also affects healthy endothelial function by loss of inherent anti-atherogenic and anti-inflammatory properties which in turn further accelerates atherogenicity and macrovascular disease.13,14 This effect in coronary arteries leads to the increased risk of myocardial infarction and ischemic cardiomyopathy. Furthermore, comorbidities commonly seen in patients with diabetes, such as hypertension, dyslipidaemia and renal impairment, also accelerate the progression of cardiovascular disease.

The microcirculation has central (sympathetic and parasympathetic) and local regulatory mechanisms.4 Endothelial dysfunction leads to imbalance between the vasodilators and vasoconstrictors that it produces, leading to an inability to promptly adjust the microvascular flow to meet the metabolic needs of the tissue.15 Subjects with diabetes have been found to have decreased bioavailability of nitric oxide, a potent vasodilator, as well as increased secretion of the vasoconstrictor, endothelin-1.13,16,17

Diabetic autonomic neuropathy also leads to impaired autoregulation of blood flow.18 Diabetic patients with disturbed autonomic function have a higher heart rate than non-diabetic patients due to decreased vagal tone. Tachycardia increases myocardial oxygen demand and reduces coronary artery perfusion due to a shortened diastole which over time increases the risk of arrhythmias and ventricular dysfunction.19 Cardiac autonomic dysfunction is also one of the presumed causes of a ‘silent myocardial infarction’ due to their decreased or even absent perception of ischaemic pain.20

Left ventricular impairment may develop regardless of typical risk factors such as hypertension and coronary artery disease in the diabetic population and this is termed diabetic cardiomyopathy.21,22 The precise cause for this has not been determined, but may include mitochondrial dysfunction, increased fibrosis, impaired calcium accumulation and inflammation.20,23,24 There is also some evidence that cardiac contractility is affected by impaired cardiac glucose metabolism and increased free fatty acid oxidation for energy metabolism; this in turn can lead to ventricular impairment.25

Recently, it has become apparent that the relationship between heart failure and diabetes is more bidirectional in nature rather than just diabetes leading to heart failure.1,2 An observational study showed diabetes developed in 29% of heart failure subjects compared with 18% of matched control subjects over three years.26 One postulated theory is that the decreased physical activity in heart failure patients may lead to decreased insulin sensitivity.2 Furthermore, neuro-humoral activation, including increased catecholamine levels and sympathetic activity stimulate gluconeogenesis and glycoegenolysis leading to hyperglycaemia.27 Poor cardiac output and increased venous congestion can cause hypoperfusion of the pancreas and the liver thereby weakening their potential to regulate metabolic homeostasis.2 Indeed, results from a recent study suggest that left ventricular assist devices improved glycaemic control in patients with diabetes.28

Heart failure drugs and their effect on blood glucose

Diuretics
Diuretics have a big role in symptom management of heart failure patients;29 however, studies have shown a positive association between diuretic use and the occurrence of diabetes.30 Researchers have suggested many potential reasons
for this, which include hypokalaemia, changes in the autonomic nervous system function, changes in the beta-cell function and insulin sensitivity as a result of diuretic use.\textsuperscript{5,21,22} Thiazides in particular have been shown to be associated with an increase in hyperglycaemia\textsuperscript{25} and therefore loop diuretics may be better tolerated in this group of patients. The symptoms of new-onset diabetes, including polyuria, polydipsia and weight loss in patients on diuretics, may be attributed to side effects of the diuretics themselves. This can delay diagnosis and potentially increase the risk of developing a diabetic emergency, particularly HHS.

**Beta blockers**

There have been concerns previously about beta blockers worsening glycaemic control and masking symptoms of hypoglycaemia;\textsuperscript{13,33} however, there have been no studies to date that prove this. On the other hand, multiple studies have shown that beta-blockers improve survival and reduce heart failure hospitalisations in patients with both diabetes and heart failure.\textsuperscript{34–36} There is some evidence that beta blockers can precipitate diabetes especially when used alongside diuretics.\textsuperscript{4,6,32} Newer vasodilating beta blockers such as carvedilol and nebivolol have less of an effect on glycaemic control.\textsuperscript{37}

**Other medications commonly used in heart failure**

ACE inhibitors (ACE-i) and angiotensin II receptor blockers (ARBs) are established therapies in heart failure. Randomised clinical trials have shown that they not only improve survival and reduce heart failure hospitalisation but can also reduce incidence of new-onset diabetes in heart failure patients.\textsuperscript{38–40}

Mineralocorticoid receptor antagonists (MRAs) have also shown prognostic benefits in heart failure studies.\textsuperscript{41,42} There have again been some concerns about the use of spironolactone (less so with eplerenone) and its effects on glycaemic control but there has been no conclusive evidence to date and further studies are needed.\textsuperscript{43,44} Newer drugs such as Entresto (a combination of sacubitril and valsartan) and ivabradine have been shown to be effective in heart failure studies in patients with and without concomitant diabetes.\textsuperscript{45,46}

**Diabetes drugs and their effect on cardiac function**

Glucose-lowering agents may promote the development of heart failure through several pathophysiological mechanisms related to increased insulin levels, water retention and low glucose availability for the myocardium. Tight glycaemic control has not been shown to reduce incidence of heart failure in studies to date,\textsuperscript{3,47–49} while hyperglycaemia has been shown to be associated with worse outcomes.\textsuperscript{50} The thiazolidinediones lead to fluid retention and, indeed, rosiglitazone was withdrawn because of the increased risk of developing heart failure while taking it. Metformin\textsuperscript{51,52} and empagliflozin\textsuperscript{53} have been shown to be safe and effective in diabetic patients with heart failure although caution needs to be exercised when using metformin in patients with renal impairment. The recent EMPA-REG OUTCOME study has shown promising results with empagliflozin leading to significant reduction in mortality and hospitalisation from heart failure.\textsuperscript{53}

**Management of hyperglycaemic emergencies in patients with heart failure**

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are two acute and life-threatening complications of diabetes requiring prompt recognition and aggressive therapy. If they have concomitant heart failure, managing these patients may well pose many challenges: managing haemodynamic compromise; fluid management; and managing associated metabolic derangements such as kidney function, associated acidemia and base excess.

The development of DKA is usually relatively acute, occurring in less than 24–48 hours, whereas HHS usually develops over several days to weeks and can lead to more profound dehydration.\textsuperscript{54} Symptoms such as polyuria, polydipsia, blurred vision, cognitive impairment, fatigue, weakness, and weight loss can be seen in both conditions. DKA patients usually present with vomiting and abdominal pain.\textsuperscript{55}

Heart failure patients with diabetics are just as susceptible to developing these conditions as the rest of the diabetic population. Some of the common causes of DKA and HHS are infections, particularly gastroenteritis; stress such as major surgery, myocardial infarction, pancreatitis or stroke; or insufficient insulin.\textsuperscript{55} Previously undiagnosed diabetes can present as DKA or HHS. Certain medications such as corticosteroids, thiazides, sympathomimetics, conventional and atypical antipsychotic drugs can also precipitate the development of DKA and HHS. It is important to note that no obvious cause of DKA and HHS is identified in nearly one-fifth of patients presenting with a hyperglycaemic emergency.\textsuperscript{35}

The mainstay of treatment of these diabetic emergencies is insulin, fluids and electrolyte correction; ideally, these patients should also be managed in a high-care setting. There are no specific guidelines to date on specific management of hyperglycaemic emergencies in heart failure although UK guidelines suggest that ‘fluid replacement may need to be modified’.\textsuperscript{56} It is important to take a focused history from the patient or their family to try to identify what might have triggered the decomposition. In addition to reviewing the patient’s last HbA\textsubscript{1c}, it would be helpful to find the patient’s latest echocardiogram, cardiology letter and previous admission history as these may all give clues to their cardiac function, fluid status and cardiac medication history. A weight taken in clinic may be helpful to assess their current fluid depletion.

Assessing volume status in these patients can be difficult. Heart failure patients can have peripheral oedema and this does not reflect their intravascular volume. Patients are often intravascularly depleted during the hyperglycaemic state while appearing peripherally overloaded. Therefore care should be taken while examining and interpreting volume status. Looking for jugular venous pressure, assessing
the extent of peripheral oedema, evidence of lung congestion (clinically and on X-ray), inferior vena cava size and collapsibility on echo, central venous pressure measurement (if available), sensation of thirst and mucous membranes appearance can all help in assessing volume status. Haemodynamic status can be assessed by blood pressure/mean arterial pressure and assessment of end-organ perfusion (urine output, conscious level, capillary refill time). It is important to remember that some of these patients have a chronically low blood pressure due to reduced cardiac output and effects of medications; therefore looking at their baseline blood pressure reading from clinic letters may guide assessment. A high urine output reflects the hyperglycaemia and does not mean the patient is well hydrated. A low urine output suggests poor renal perfusion. Blood tests may include venous blood glucose, ketones, blood gas, serum osmolality (calculated or measured) and troponin if clinically indicated. The role of brain natriuretic peptide (BNP) in these situations would be difficult to interpret and as such there is no role currently in BNP guided management. An ECG should be performed in all patients.

Specific management of associated abnormalities

Fluid balance

Both DKA and HHS are associated with large fluid and electrolyte deficits. The severity of dehydration is greater in HHS than in DKA. Fluid replacement is crucial for the restoration of intravascular, interstitial and intracellular volume and renal perfusion. The average fluid deficit is approximately 5–7 litres in DKA but may be as much as 22 litres in HHS. For DKA, UK guidelines suggest one litre of fluid over the first hour then 500ml/hour over the next 4 hours. In HHS, the guidelines suggest replacing half of the fluid deficit in the first 12 hours and the other half in the following 12 hours. Such large volume administration can decompensate heart failure patients.

Normal saline (0.9% sodium chloride) with potassium added as required is the preferred fluid in both DKA and HHS, as the main electrolyte losses are of sodium, chloride and potassium. A Cochrane review recommended use of crystalloid fluids rather than colloid in ill patients. The use of Ringer’s lactate (Hartmann’s solution) in HHS or in DKA failed to show benefit compared to normal saline.

In patients with heart failure a more cautious approach is required. Giving 1–1.5 litres of normal saline over 1–2 hours with frequent haemodynamic and clinical monitoring could be attempted as initial resuscitation. Further fluid resuscitation should be tailored to the patient’s clinical status and response. If there are signs of worsening haemodynamics, for example low blood pressure or evidence of poor perfusion such as cool peripheries or poor urine output, then this might warrant use of vasoactive drugs and escalation of treatment to a critical care setting.

Remote impairment

Blood tests in these patients may reveal renal impairment. This could be due to many reasons including diabetic nephropathy, heart failure (i.e. cardio-renal syndrome), dehydration and medications. It is important to go through previous results and identify baseline renal function. Depending on the degree of derangement and clinical assessment, it may be necessary to withhold some of the prognostic heart failure medications such as ACE-i and MRAs and adjust diuretics to aid patients’ recovery from the acute phase. Measuring urine output and recording daily weights (if possible) further aids management. When the patient is stable and over the acute phase, it is important to restart and to up-titrate these drugs to target doses as tolerated. The hospital heart failure team should be involved in the patient’s management as soon as possible.

Metabolic derangement

It is important to remember acidosis and acidemia are cardiac suppressants. Some degree of acidosis can be seen in HHS and DKA patients owing to their poor cardiac output, increased anaerobic metabolism, glucose and ketones, metformin, poor renal function and liver hypo-perfusion. It is also important that

Practice points for fluid management in patients with heart failure presenting with hyperglycaemic emergencies

- Fluid management can be difficult in these patients; accurate and recurrent assessment of fluid status is crucial.
- Remember heart failure patients may appear peripherally overloaded while being intravascularly depleted during the hyperglycaemia state.
- Previous records of weight, echo findings and fluid status may be helpful.
- Normal saline with potassium is the fluid of choice.
- A more cautious approach of giving 1–1.5 litres of normal saline over 1–2 hours with frequent haemodynamic and clinical monitoring could be attempted as initial resuscitation in patients with heart failure.
- Fluid resuscitation should be tailored to patients’ clinical status and response. If there are signs of worsening haemodynamics, this might warrant use of vasoactive drugs and escalation of treatment to a critical care setting.
care be taken in correcting acidosis gently, if hyperglycaemia is the primary cause of the acidosis. Bicarbonate should not be given to correct the metabolic derangement as it can worsen central nervous system acidosis and precipitate cerebral oedema.\textsuperscript{36}

**Electrolyte imbalance**
Abnormalities in sodium and potassium are common. This can be because of the volume status and acute shifts between intra- and extracellular spaces in hyperglycaemic states. However, in patients with heart failure medications such as ACE-i, diuretics and MRAs can also be causative. Often the admission sodium is low because of the hyperglycaemia. Modern analysers do not give pseudo-hypernatraemia with hyperlipidaemia but the low sodium with hyperglycaemia is real in order to preserve osmolality. As a result, a normal or high measured serum sodium in this setting indicates a severe state of dehydration, as is often the case in patients presenting with HHS. Similarly, an extracellular shift of potassium caused by insulin deficiency, acidemia and hyperglycemia may increase the patient’s serum potassium. However, a high measure of serum potassium in this setting may be falsely reassuring as the body’s total potassium stores may in reality be depleted. Renal impairment and heart failure medications such ACE-i, ARBs and MRAs can also cause hyperkalaemia. A low potassium level therefore suggests severe total body potassium depletion.

**Thromboembolic state**
During the acute phase of a hyperglycaemic emergency, patients are at risk of clot formation due to the associated hyper-viscosity of blood. This is further worsened by poor cardiac output in patients with concomitant heart failure. Therefore thromboembolism prophylaxis should be administered in all patients unless there is a significant contraindication.

**Summary**
Patients with concomitant heart failure and diabetes have diverse pathophysiological, metabolic and neuro-hormonal abnormalities that potentially contribute to worse outcomes than those without comorbid diabetes. Hyperglycaemic emergencies such as DKA and HHS are associated with a high mortality risk. Managing such acute emergencies in patients with diabetes and heart failure can be challenging, particularly in assessing fluid status correctly. It is important to involve both diabetologists and cardiologists as soon as possible to ensure the best outcome for patients.

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**Declaration of interests**
There are no conflicts of interest declared.

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