Clinical Medicine 2012, Vol 12, No 3: 272–5

CME Acute Medicine

Edited by Derek Bell, professor of acute medicine, Imperial College London and NIHR CLAHRC for Northwest London

Hyperglycaemia in the acute care setting

Anjali Balasanthiran, *clinical research fellow & specialist registrar in diabetes & endocrinology, NIHR CLAHRC for North West London and Westminster Hospital, London;* **Ben Zalin**, *consultant in acute medicine, diabetes & endocrinology, Lister Hospital, Stevenage;* **Emma H Baker**, *professor of clinical pharmacology, St George's Hospital, University of London;* **Kevin Shotliff**, *consultant physician, Chelsea and Westminster Hospital, and honorary senior lecturer, Imperial college, London*

Hyperglycaemia is common in the acute care setting. In a study of 2,030 adults admitted acutely to hospital, 32% of whom had no prior history of diabetes mellitus (DM), 38% had a fasting blood glucose above 7.0 mmol/l or a random glucose above 11.1 mmol/l.[1] Patients with acute hyperglycaemia with no prior diagnosis of diabetes may either have stress hyperglycaemia precipitated by the physiological stress of acute illness or undiagnosed DM. This article provides an overview of the mechanisms, impact and diagnosis of acute hyperglycaemia and outlines recommendations for treatment and follow-up.

Pathophysiology

Mechanisms underlying stress hyperglycaemia include increased release of counter-regulatory hormones and pro-inflammatory cytokines, leading to a rise in insulin resistance and gluconeogenesis. Specific treatments such as glucocorticoids or enteral nutrition, as well as underlying poor pancreatic reserve or insulin resistance, increase the risk of stress hyperglycaemia. A vicious cycle then develops, with hyperglycaemia exacerbating inflammation and oxidative stress which drive worsening hyperglycaemia.[2]

Impact of acute hyperglycaemia

Acute hyperglycaemia may be an immediate life-threatening emergency due to decompensated or undiagnosed diabetes or a stress response to acute illness (stress hyperglycaemia). Stress hyperglycaemia is also associated with poor outcomes. Patients with hyperglycaemia may be asymptomatic or experience classic symptoms of polyuria, polydipsia and lethargy. Where hyperglycaemia is prolonged, patients may also report recurrent infections, weight loss and blurred vision.

It is crucial to identify hyperglycaemic emergencies such as diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar syndrome (HHS) and treat rapidly according to national guidelines. The management of stress hyperglycaemia is less clearly defined and remains the subject of research.

Hyperglycaemic emergencies

Diabetic ketoacidosis

DKA is a complex disordered metabolic state characterised by hyperglycaemia, acidosis and ketonaemia,[3] most commonly occurring in patients with new or known type 1 DM due to insulin deficiency or inadequate insulin replacement. Although most often seen in younger people, DKA can occur in elderly patients with long-standing type 1 diabetes. It can also affect patients with type 2 diabetes with relative insulin deficiency (ketosis-prone type 2 diabetes) in combination with severe illness. Clinical features include polyuria, polydipsia, hyperventilation and abdominal pain. Recommended management includes urgent replacement of insulin and fluids, guided by venous (rather than arterial) bicarbonate and pH, with blood ketone testing (using bedside meters).[3]

Hyperglycaemic hyperosmolar syndrome

HHS typically presents in older patients with type 2 diabetes and has a high mortality. It is characterised by hyperosmolality and dehydration without significant ketoacidosis. Other common clinical features include lethargy and neurological deficit. Management priorities include rehydration, thromboprophylaxis and treatment of any precipitating cause (often infection).

Stress hyperglycaemia

Elevated blood glucose during acute illness is associated with poor outcomes from diverse conditions including myocardial infarction (MI),[4,5] stroke[6] and respiratory infection.[7,8] The relationship between blood glucose and poor outcomes is continuous, so it is difficult to identify a cut-off value above which blood glucose levels are considered abnormal. However, a reasonable definition for stress hyperglycaemia is random blood glucose above 7.0 mmol/l. Acute hyperglycaemia has a greater adverse impact on outcomes in patients without prior DM than in those with diabetes.[1,5] At present it is not clear whether hyperglycaemia directly causes poor outcomes or is simply a marker of acute illness severity. Potential adverse effects of hyperglycaemia include increased oxidative stress, impaired endothelial function and activation of the coagulation pathway.

Hyperglycaemia in acute coronary syndrome

In all patients with MI, admission glucose is a strong predictor of increased mortality and in-hospital complications. A review of 15 studies found that the relationship between hyperglycaemia and poor outcomes was particularly strong for patients without prior diabetes.[5] In non-diabetic patients, risk of death post-MI was 3.9 times greater in those with admission blood glucose 6.1–8.0 mmol/l, and risk of heart

failure or cardiogenic shock three-fold higher in those with admission glucose 8–10 mmol/l than in those with lower admission glucose levels.[5] Similarly, persistently elevated glucose levels during admission are associated with increased in-hospital mortality.[9]

Despite a clear association between hyperglycaemia and poor outcomes, studies of intensive glycaemic control in acute MI (including the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) and the Hyperglycaemia: Intensive Insulin Infusion in Infarction (HI-5) studies) have failed to identify an optimal treatment strategy. Factors that may account for conflicting trial evidence include inadequate patient recruitment and glucose control. In this context, the National Institute for Clinical Excellence recommends initiating treatment with a dose-adjusted insulin infusion in patients admitted to hospital with ACS when blood glucose is above 11.0 mmol/l.

A significant proportion of individuals with hyperglycaemia during ACS will have undiagnosed diabetes or glucose intolerance. All patients with hyperglycaemia without prior diagnosis of diabetes should therefore be offered:[9]

- glycosylated haemoglobin (HbA_{1c}) test before discharge
- fasting glucose test no earlier than four days after onset of ACS
- lifestyle advice
- counselling regarding symptoms of hyperglycaemia
- annual general practitioner monitoring of HbA_{1c} and fasting glucose levels.

Hyperglycaemia in stroke

Hyperglycaemia is a common finding in acute ischaemic stroke – reported in 32% of patients without prior diabetes.[10] A systematic review concluded that high glucose levels predict increased in-hospital mortality and poor functional recovery in stroke survivors.[11] Hyperglycaemia may exacerbate brain injury and induce cell lysis in metabolically-challenged tissue through a variety of mechanisms, including:

- anaerobic metabolism
- free radical generation, and
- increased blood-brain-barrier permeability.[12]

To date, only one underpowered clinical trial has investigated the effect of glycaemic control on stroke outcome, finding no clinical benefit.[13] Despite this, and perhaps in view of the available theoretical evidence,[12] various guidelines advocate the treatment of hyperglycaemia in this population (Table 1).

Hyperglycaemia in respiratory infection

Acute hyperglycaemia is particularly common in patients with exacerbations of chronic obstructive pulmonary disease (COPD) due to physiological stress, underlying impaired glucose intolerance and treatment with oral glucocorticoids. In two separate studies, 50% of patients hospitalised with acute COPD exacerbations had random blood glucose of 7 mmol/l or above. Each 1 mmol/l increase in blood glucose increased absolute risk of death or prolonged hospital stay by 15%.[8] Hyperglycaemia also predicts failure of non-invasive ventilation after initial success.[15] Prospective studies are currently underway to determine whether blood glucose control can improve COPD exacerbation outcomes.

Hyperglycaemia in diabetes mellitus

Prior diagnosis of diabetes

Patients with diabetes accounted for 9.7% of all inpatients in one UK hospital. It is well recognised that the stress of acute illness may exacerbate hyperglycaemia in this population. Acute adjustments in therapy may be required to control blood glucose. Any adjustments should be monitored following resolution of the acute illness to avoid subsequent overtreatment.

Table 1. Summary of international recommendations for treatment of hyperglycaemia in acute stroke.

Organisation	Recommendation
NICE[14]	People with acute stroke should be treated to maintain blood glucose 4–11 mmol/l
European Stroke Initiative	Glucose values >10 mmol/l should be treated
AHA/ASA	Treat patients with insulin if serum glucose concentrations 7.8 mmol/l
	Close monitoring to avoid hypoglycaemia recommended

AHA = American Heart Association; ASA = American Stroke Association; NICE = National Institute for Health & Clinical Excellence.

Key points

Hyperglycaemia is common in the acute care setting, reflecting high prevalence of known or undiagnosed diabetes mellitus (DM) and the physiological effects of acute illness, causing 'stress hyperglycaemia'

There is a continuous association between increasing blood glucose concentrations and worsening clinical outcomes in diverse acute illnesses although causality has not been proven

UK guidelines currently recommend blood glucose control in patients admitted with acute coronary syndrome or stroke

Patients with acute hyperglycaemia without a prior diagnosis of DM should have HbA1c measured both prior to discharge to determine diagnosis or risk of diabetes and at subsequent follow-up

KEYWORDS: acute, critical care, chronic obstructive pulmonary disease, myocardial infarction, stress hyperglycaemia, stroke

Table 2. Investigations commonly used to identify hyperglycaemia/new-onset diabetes mellitus in the acute setting.

Investigation	Comments
Capillary blood glucose measurement	Measured at the bedside
	Commonly checked early in acute admission, may be overlooked by admitting team if result is filed in emergency notes
	Mostly used for monitoring patients with previously abnormal blood glucose concentrations and/or at high risk of diabetes
	Less accurate at very low and high glucose concentrations, but useful as an indicator of glucose abnormalities in emergency situations (eg seizures, altered consciousness, coma, cardiac arrest and hyperglycaemic or hypoglycaemic emergencies)
Arterial/venous blood gas analysis	Presents an opportunity to check glucose levels in patients with acute illness requiring blood gas analysis (eg sepsis, COPD)
Fasting plasma glucose concentration*	Taking fasting samples may be difficult in the acute care setting
	If symptoms of diabetes are present (polyuria, polydipsia, unexplained weight loss), a diagnosis of diabetes can be made in the acute setting based on a single fasting glucose concentration ≥7.0 mmol/l
	Fasting plasma glucose is not useful in suspected steroid-induced diabetes where hyperglycaemia is typically post-prandial
Random plasma glucose concentration*	Pragmatically easier to obtain than fasting samples in the acute setting
	If symptoms of diabetes are present, a diagnosis of diabetes can be made in the acute setting based on a single random glucose concentration ≥11.1 mmol/l
HbA_{1c} †	HbA_{1c} gives an estimate of blood glucose over about 3 months. Thus elevated HbA_{1c} can be used to determine chronicity of hyperglycaemia in acutely unwell patients and may now be used to diagnose type 2 diabetes† (see Table 3)

*In the absence of symptoms, diagnosis requires two abnormally high glucose results.
†WHO now recommend that HbA1c can be used as a diagnostic test for type 2 diabetes if the following conditions are met: stringent quality assurance tests in place, assays standardised to criteria aligned to the international reference values and no conditions present precluding accurate measurement (for further details see annex 1 of WHO report17).
COPD = chronic obstructive pulmonary disease; HbA_{1c} = glycosylated haemoglobin.

Table 3. Interpretation of glycosylated haemoglobin (HbA1c) values.

- HbA_{1c} ⩾48 mmol/mol (6.5 %): diabetes mellitus,[18] needs follow-up*
- HbA_{1c} 42–47 mmol/mol (6.0–6.4 %): high risk of diabetes mellitus, needs follow-up*[19]
- HbA_{1c} <42 mmol/mol (<6.0 %): follow-up of acute hyperglycaemia at discretion of clinician; consider whether patient has other risk factors for diabetes[19]
- It is important to note that HbA_{1c} <48 mmol/mol (<6.5 %) does not exclude diabetes diagnosed using glucose tests.[18]

* See Table 4.

Table 4. Recommended follow-up for patients with hyperglycaemia in the acute setting.

Diagnosis	Follow-up
Known diabetes mellitus	Monitor glucose levels up to discharge
	Review and adjust treatment following resolution of acute illness
	Increased treatment may need to be reduced at or after discharge
	Ensure community support from GP, diabetes specialist nurse, community diabetes team as required
Newly diagnosed diabetes*	Patient education
	Diabetes team review
	Follow-up with GP, diabetes clinic, dietitian, diabetes specialist nurse
	Future foot and eye screening as appropriate
High diabetes risk - HbA_{1c}*	Provide intensive lifestyle advice
	Warn patients to report symptoms of diabetes
	Monitor HbA_{1c} annually[19]

* see Tables 2 and 3.
GP = general practitioner; HbA_{1c} = glycosylated haemoglobin.

Undiagnosed diabetes mellitus

It is estimated that about half a million people in the UK have undiagnosed diabetes. Hyperglycaemia in the acute setting presents an opportunity to identify these individuals and offer appropriate treatment to delay or prevent the onset of diabetic complications. Given that diabetes is a risk factor for macrovascular disease, acute admissions with stroke, transient ischaemic attack, ACS or peripheral vascular disease should prompt investigation. Other populations at risk of diabetes include those who are obese or taking oral corticosteroids. Recent US guidelines recommend that all patients should undergo laboratory glucose testing on admission.[17]

Diagnosis of diabetes mellitus in the acute care setting

Some measurements taken in acute care and their utility are described in Tables 2 and 3. Stress hyperglycaemia is common, so fasting and random blood glucose measurements in the first few days of acute illness may not be discriminatory in the absence of symptoms. An elevated HbA_{1c} will indicate chronic hyperglycaemia preceding the acute illness, but a 'normal' HbA_{1c} does not exclude DM. All patients without diabetes found to have hyperglycaemia in the acute setting should be reviewed on recovery to identify underlying glucose tolerance and determine whether any treatment is necessary (Table 4).

Conclusions

Hyperglycaemia in the acute setting is common and frequently overlooked. In all contexts, acute hyperglycaemia is associated with poor clinical outcomes. Pragmatic guidelines for the treatment of acute hyperglycaemia exist, but further research and improved clinical awareness are required to reduce adverse outcomes and increase the pick-up of undiagnosed diabetes in the acute setting.

References

1 Umpierrez GE, Isaacs SD, Bazargan N *et al.* Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978–82.

2 Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009;373:1798–807.

3 Diabetes UK. *The management of diabetic ketoacidosis in adults.* Joint British Diabetes Societies Inpatient Care Group, March 2010.

4 Deedwania P, Kosiborod M, Barrett E *et al.* Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. AHA Scientific Statement. *Circulation* 2008;117:1610–9.

5 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355:773–8.

6 Samiullah S, Qasim R, Imran S, Mukhtair J. Frequency of stress hyperglycaemia and its influence on the outcome of patients with spontaneous intracerebral haemorrhage. *J Pak Med Assoc* 2010;60:660–3.

7 McAlister FA, Majumdar SR, Blitz S *et al.* The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community acquired-pneumonia. *Diabetes Care* 2005;28:810–5.

8 Baker EH, Janaway CH, Phillips BJ *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006;61:284–9.

9 National Institute for Health and Clinical Excellence. *Hyperglycaemia in acute coronary syndromes.* NICE clinical guideline CG130, October 2011.

10 Allport L, Baird T, Butcher K *et al.* Frequency and temporal profile of post-stroke hyperglycemia using continuous glucose monitoring. *Diabetes Care* 2006;29:1839–44.

11 Capes SE, Hunt D, Malmberg K, Patna P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001;32:2426–32.

12 Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. *Stroke* 2004;35:363–4.

13 Gray CS, Hildreth AJ, Sandercock PA *et al.* Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007;6:397–406.

14 National Institute for Health and Clinical Excellence. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE clinical guideline CG68, July 2008.

15 Moretti M, Cilione C, Tampieri *et al.* Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax* 2000;55:819–25.

16 Sampson MJ, Crowle T, Dhatariya K *et al.* Trends in bed occupancy for inpatients with diabetes before and after the introduction of a diabetes inpatient specialist nurse service. *Diabet Med* 2006;23:1008–15.

17 Umpierrez GE, Hellman R, Korytkowski MT *et al.* Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2012;97:16–38.

18 Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO/IDF consultation, January 2011.

19 Diabetes UK. New Diagnostic Criteria for Diabetes and Practical Guidance: http://www.diabetes.org.uk/About_us/Our_Views/Care_recommendations/New_diagnostic_criteria_for_diabetes_/. Jan 2011

Address for correspondence:
Dr A Balasanthiran, NIHR CLAHRC for Northwest London, 4th floor lift bank D, 369 Fulham Road, Chelsea and Westminster Hospital, London SW10 9NH.
Email: a.balasanthiran@imperial.ac.uk