

Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia

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Abstract | Diabetic ketoacidosis (DKA), hyperglycaemic hyperosmolar state (HHS) and hypoglycaemia are serious complications of diabetes mellitus that require prompt recognition, diagnosis and treatment. DKA and HHS are characterized by insulinopaenia and severe hyperglycaemia; clinically, these two conditions differ only by the degree of dehydration and the severity of metabolic acidosis. The overall mortality recorded among children and adults with DKA is <1%. Mortality among patients with HHS is ~10-fold higher than that associated with DKA. The prognosis and outcome of patients with DKA or HHS are determined by the severity of dehydration, the presence of comorbidities and age >60 years. The estimated annual cost of hospital treatment for patients experiencing hyperglycaemic crises in the USA exceeds US\$2 billion. Hypoglycaemia is a frequent and serious adverse effect of antidiabetic therapy that is associated with both immediate and delayed adverse clinical outcomes, as well as increased economic costs. Inpatients who develop hypoglycaemia are likely to experience a long duration of hospital stay and increased mortality. This Review describes the clinical presentation, precipitating causes, diagnosis and acute management of these diabetic emergencies, including a discussion of practical strategies for their prevention.

Diabetic ketoacidosis (DKA), hyperglycaemic hyperosmolar state (HHS) and hypoglycaemia are frequent and serious complications arising among patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). In the USA, ~145,000 cases of DKA occur each year^{1,2}. The rate of hospitalization for HHS is lower, accounting for <1% of all diabetes-related admissions^{3,4}. The frequency of emergency room visits for hypoglycaemia is similar to that reported for severe hyperglycaemia^{1,5}. Among hospitalized individuals, hypoglycaemia is a frequent complication of ongoing treatment for hyperglycaemia, with a reported incidence of 5–28% in intensive care unit (ICU) trials (depending on the intensity of glycaemic control)⁶, and 1–33% in non-ICU trials using subcutaneous insulin therapy^{7,8}.

DKA, HHS and hypoglycaemia are associated with substantial morbidity and mortality, as well as high healthcare costs. DKA is the leading cause of mortality among children and young adults with T1DM, accounting for ~50% of all deaths in this population⁹. The overall DKA mortality recorded in the USA is <1%^{1,2}, but a higher rate is reported among patients aged >60 years and individuals with concomitant life-threatening illnesses^{1,2,9,10}. Death occurs in 5–16% of patients with

HHS^{4,11}, a rate that is ~10-fold higher than that reported for DKA^{4,12}. Similarly, hypoglycaemia is associated with twofold to threefold increased mortality, particularly as age increases and among patients who have a history of severe hypoglycaemic episodes¹³. Several studies have reported that mortality in hyperglycaemic states is not caused by metabolic disarray but rather reflects the precipitating factor^{14,15}. In the case of hypoglycaemia, in-hospital mortality is reported as being more frequent among patients with spontaneous hypoglycaemia than among those with insulin-induced or iatrogenic hypoglycaemia; however, these claims have been disputed^{16–19}. Treatment of diabetic emergencies represents a substantial economic burden. For example, in the USA, the average cost of managing DKA is US\$17,500 per patient, which represents a total annual hospital cost of \$2.4 billion¹. Similarly, hypoglycaemia is associated with immediate and delayed adverse clinical outcomes, as well as an increase in economic costs^{20–22}.

This Review describes the clinical presentation, precipitating causes, diagnosis and acute management of DKA, HHS and hypoglycaemia, including a discussion of practical approaches to prevent the onset of these diabetic emergencies.

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Key points

- Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) are serious acute metabolic complications of diabetes mellitus, representing points along a spectrum of hyperglycaemic emergencies caused by poor glycaemic control
- DKA comprises hyperglycaemia, hyperketonaemia and metabolic acidosis; diagnostic criteria for HHS include a plasma glucose level >33.3 mmol/L, serum osmolality >320 mmol/kg and no appreciable metabolic acidosis and ketonaemia
- Management objectives for DKA and HHS include restoration of circulatory volume and tissue perfusion; correction of hyperglycaemia, ketogenesis and electrolyte imbalance; and identification and treatment of the precipitating event
- Hypoglycaemia is defined as a blood glucose level <3.9 mmol/L in both the inpatient and outpatient settings
- Severe hypoglycaemic events can negate the beneficial effects of intensive glycaemic management strategies that target near normoglycaemia among patients with diabetes mellitus
- Patient and family education regarding the signs and symptoms of hypoglycaemia, as well as the methods available for treatment, can effectively reduce the risk of severe hypoglycaemic episodes

DKA and HHS

Precipitating causes

DKA. TABLE 1 outlines the most common precipitating causes of DKA worldwide, as determined by epidemiological studies. In the USA and other developed nations, the most frequently reported precipitating causes are poor adherence to insulin therapy, infection and newly diagnosed diabetes mellitus. By contrast, infections and poor access to care are the most prevalent precipitating causes in developing nations.

Drugs that affect carbohydrate metabolism, such as corticosteroids, sympathomimetics and atypical antipsychotics, might also precipitate the development of DKA^{1,14,23}. In addition, an association has been reported between the use of sodium–glucose co-transporter 2 (SGLT2) inhibitors (a class of oral antidiabetic agents that decrease concentrations of plasma glucose by inhibiting proximal tubular reabsorption in the kidney) and the development of DKA among patients with T1DM and T2DM^{24,25}.

HHS. HHS is the initial manifestation of diabetes mellitus in 7–17% of patients; however, this complication is more often reported in the setting of previously diagnosed diabetes mellitus^{14,26}. Infection is the major precipitating cause in 30–60% of patients with HHS, followed by omission of

insulin or other antidiabetic medications and the presence of concomitant illnesses, such as cerebrovascular events, myocardial infarction and trauma^{14,26}.

Pathophysiology

Both DKA and HHS result from absolute or relative insulin deficiency in association with increased circulating levels of glucagon and other counter-regulatory hormones (catecholamines, cortisol and growth hormone), all of which oppose the action of any residual circulating insulin^{14,26}. This hormonal milieu promotes increased hepatic glucose production, decreased peripheral insulin sensitivity and hyperglycaemia.

Severe insulin deficiency correlates with increased activity of the hormone-sensitive lipase in adipose tissue, which in turn leads to the breakdown of triglycerides into glycerol and high circulating levels of free fatty acids²⁷. In the liver, free fatty acids are oxidized to ketone bodies, a process predominantly stimulated by glucagon²⁸. Increased concentrations of glucagon lower hepatic levels of malonyl coenzyme A (CoA), the first rate-limiting enzyme in *de novo* fatty acid synthesis. Decreased levels of malonyl-CoA then stimulate the rate-limiting enzyme of ketogenesis (carnitine O-palmitoyltransferase 1, liver isoform (CPT1-L)), which promotes transesterification of fatty acyl carnitine and oxidation of free fatty acids to ketone bodies (acetoacetate and β -hydroxybutyrate)²⁹. Thus, production of ketone bodies is accelerated as a result of increased fatty acyl CoA and CPT1-L activity^{29,30}. In addition, metabolism and clearance of ketone bodies are decreased in states of DKA. Ketone bodies are strong acids that, when present at high levels, can cause metabolic acidosis. Both hyperglycaemia and high levels of ketone bodies cause osmotic diuresis, which leads to hypovolaemia and decreased glomerular filtration rate, the latter of which further aggravates hyperglycaemia¹⁴.

Patients with HHS are also insulin-deficient; however, they exhibit higher insulin concentrations (demonstrated by basal and stimulated C-peptide levels) than do patients with DKA^{26,31}. Furthermore, patients with HHS have lower concentrations of free fatty acids, cortisol, growth hormone and glucagon than do patients with DKA³¹. The slower onset of HHS (several days) versus DKA (<1–2 days) results in more severe manifestations of hyperglycaemia, dehydration and plasma hyperosmolality, all of which correlate with impaired levels of consciousness²⁶.

Table 1 | Precipitating causes of diabetic ketoacidosis

Precipitating cause	Australia ¹¹⁵	Brazil ¹¹⁶	China ¹¹⁷	Indonesia ¹¹⁸	Korea ¹¹⁹	Nigeria ¹²⁰	Spain ¹²¹	Syria ¹²²	Taiwan ¹²³	USA ^{15,23}
New diagnosis of diabetes mellitus, %	5.7	12.2	NR	3.3	NR	NR	12.8	NR	18.2	17.2–23.8
Infection, %	28.6	25.0	39.2	58.3	25.3	32.5	33.2	47.8	31.7	14.0–16.0
Poor adherence to treatment, %	40.0	39.0	24.0	13.3	32.7	27.5	30.7	23.5	27.7	41.0–59.6
Other, %	25.7	15.0	10.9	17.1	11.2	4.8	23.3	7.8	6.2	9.7–18.0
Unknown, %	NA	8.8	25.9	8.0	30.8	34.6	NA	20.9	16.2	3.0–4.2

NA, not applicable; NR, not reported.

Diagnosis

A diagnosis of DKA or HHS should be suspected in every ill patient with hyperglycaemia.

DKA. Patients with DKA usually present within hours to days of developing polyuria, polydipsia and weight loss. Nausea, vomiting and abdominal pain are detected in 40–75% of cases³². Physical examination reveals signs of dehydration, changes in mental status, hypothermia and the scent of acetone on the patient's breath. A deep laboured breathing pattern (Kussmaul respirations) is observed among patients with severe metabolic acidosis.

As outlined in TABLE 2, DKA comprises a triad of hyperglycaemia, hyperketonaemia and metabolic acidosis. The condition can be classified as mild, moderate or severe, depending on the extent of metabolic acidosis and alterations in the sensorium or mental obtundation. The key diagnostic criterion is an elevation in the serum concentration of ketone bodies. Although the majority of patients with DKA present with plasma glucose levels >16.7 mmol/l, some patients exhibit only mild elevations in plasma glucose levels (termed 'euglycaemic DKA') after withholding or decreasing the dose of insulin in the context of reduced food intake or illness. Euglycaemic DKA is also observed during pregnancy, among patients with impaired gluconeogenesis owing to alcohol abuse or liver failure, and among patients treated with SGLT2 inhibitors^{15,25,33}. Thus, plasma glucose levels do not determine the severity of DKA.

Confirmation of increased ketone body production is performed using either the nitroprusside reaction or direct measurement of β -hydroxybutyrate¹⁴. The nitroprusside reaction provides a semiquantitative estimation of acetoacetate and acetone levels in the plasma or urine, but does not detect the presence of β -hydroxybutyrate, which is the predominant ketone body among patients with DKA³⁴. Although more expensive than evaluation of urinary ketone bodies, direct measurement of β -hydroxybutyrate — either via a laboratory service or through use of a point-of-care metre — is the preferred option to diagnose ketoacidosis (≥ 3 mmol/l), as well as to follow the patient's response to treatment^{15,35,36}.

HHS. The diagnostic criteria for HHS include a plasma glucose level >33.3 mmol/l, an effective serum osmolality >320 mmol/kg and the absence of appreciable metabolic acidosis and ketonaemia¹ (TABLE 2). By contrast to the original formula used to estimate total serum osmolality ($2[\text{Na}] + [\text{Glucose}]/18 + [\text{BUN}]/2.8$, where [Glucose] and [BUN] are measured in mg/dl)^{4,37}, some reports and consensus guidelines have recommended the use of effective serum osmolality ($2[\text{measured Na}^+ \text{ in mEq/l}] + [\text{glucose in mmol}]$), not taking urea into consideration, as it is distributed equally in all body compartments and its accumulation does not induce an osmotic gradient across cell membranes^{1,14}. Symptoms of encephalopathy are usually present when serum sodium levels exceed 160 mmol/l and when the calculated effective osmolality is >320 mmol/kg¹⁵. Estimates suggest that ~20–30% of patients who present with HHS exhibit increased anion gap metabolic acidosis as the result of concomitant ketoacidosis, either alone or in combination with increased serum levels of lactate.

Management at presentation

Considerable variability exists in the presentation of patients with DKA and HHS. FIGURE 1 outlines the treatment algorithm for DKA and HHS recommended in the 2009 American Diabetes Association consensus statement¹. Management objectives include restoration of circulatory volume and tissue perfusion, cessation of ketogenesis, correction of electrolyte imbalances and resolution of hyperglycaemia. Many patients with DKA can be safely managed in intermediate care units unless they present with severe alteration of mental status or with critical illnesses (for example, myocardial infarction, gastrointestinal bleeding or sepsis) that require treatment in the ICU. The decision as to where affected individuals are treated is often based on the availability of adequate nursing personnel to carefully monitor the patient and to manage the insulin and intravenous fluid administration required for successful resolution of DKA. Owing to increased risk of mortality and the presence of comorbidities, most patients with HHS are treated in the ICU.

Table 2 | **Diagnostic criteria for diabetic ketoacidosis and hyperglycaemic hyperosmolar state**

Measure	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose level, mmol/l	13.9	13.9	13.9	33.3
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Bicarbonate level, mmol/l	15–18	10–14	<10	>15
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive	Negative or low positive
Urine or blood β -hydroxybutyrate, mmol/l	>3	>3	>3	<3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable	>320
Anion gap, mmol/l	>10	>12	>12	<12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma	Stupor or coma

Coexistence of DKA and HHS is reported in up to 30% of cases. *Defined as $2[\text{measured Na}^+ \text{ (mEq/l)}] + [\text{glucose (mmol)}]$. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycaemic hyperosmolar state. © 2009 American Diabetes Association. From *Diabetes Care*®, Vol. 32, 2009; 1335–1343. Modified by permission of *The American Diabetes Association*.

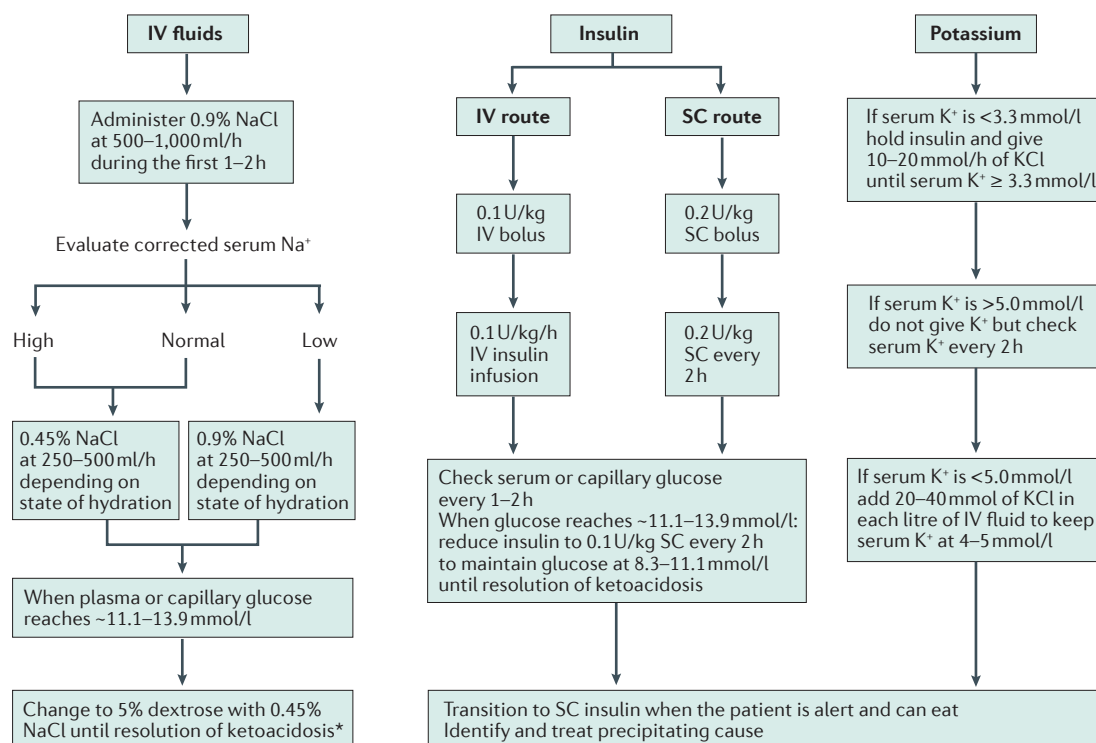


Figure 1 | Protocol for management of adult patients with diabetic ketoacidosis and hyperglycaemic hyperosmolar state recommended by the ADA. Treatment includes the administration of intravenous fluids to correct dehydration and restore tissue perfusion, insulin administration to correct hyperglycaemia and increased lipolysis and ketogenesis, and electrolyte replacement. *Defined as a blood glucose level <13.9 mmol/l, bicarbonate level >18 mmol/l and arterial or venous pH >7.3. ADA, American Diabetes Association; IV, intravenous; SC, subcutaneous. © 2009 American Diabetes Association. From *Diabetes Care*[®], Vol. 32, 2009; 1335–1343. Modified by permission of *The American Diabetes Association*.

Fluids. Replacement of lost fluids is the critical first step in the management of both DKA and HHS³⁸. The estimated water deficit is ~100 ml/kg of body weight among patients with DKA¹⁴ and ~100–200 ml/kg among patients with HHS^{26,39}. The water deficit is estimated as follows: water deficit = (0.6)(body weight in kg) × (1 – [corrected sodium/140])¹⁴. Fluid therapy restores intravascular volume and renal perfusion and reduces the level of counter-regulatory hormones and hyperglycaemia. Isotonic saline is infused at a rate of 500–1000 ml/h during the first 2–4 h, followed by the infusion of 0.9% saline at 250–500 ml/h or 0.45% saline, depending on the serum sodium concentration and the state of hydration¹⁴ (BOX 1). Once the plasma glucose level reaches ~11.1–13.9 mmol/l, replacement fluids should contain 5–10% of dextrose to allow continued insulin administration until ketonaemia is controlled, while avoiding hypoglycaemia¹.

Insulin. Following the initiation of intravenous fluids, insulin administration is the next essential step in restoring cellular metabolism, reducing hepatic gluconeogenesis and suppressing lipolysis and ketogenesis³⁸. Insulin administration by the intravenous, intramuscular or subcutaneous routes is safe and effective for correcting DKA (FIG. 1). Continuous intravenous infusion of regular human insulin is the treatment of choice among critically ill patients and those with a reduced level of consciousness (mentally obtunded).

Most treatment algorithms recommend administration of an intravenous bolus dose of 0.1 U/kg, followed by continuous intravenous infusion of 0.1 U/kg/h (5–10 U/h)¹. The necessity of the initial bolus has been called into question by one study that demonstrated no differences in outcomes or hypoglycaemia risk among a group of 157 patients who either did or did not receive an initial insulin bolus⁴⁰. Several studies have shown that insulin administration and force hydration results in a fairly predictable decrease in plasma glucose concentration at a rate of 3.6–6.9 mmol/l/h^{15,41,42}. The insulin rate should be decreased to 0.05 U/kg/h and dextrose should be added to the intravenous fluids when the plasma glucose concentration reaches ~11.1–13.9 mmol/l. The insulin infusion rate should be adjusted to maintain a plasma glucose level of 8.3–11.1 mmol/l until ketoacidosis is resolved, as evidenced by normalization of venous pH and anion gap. Insulin infusion should be continued among patients with HHS until mental obtundation and the hyperosmolar state are corrected.

The use of subcutaneous rapid-acting insulin analogues (lispro^{43–45} or aspart⁴⁶), administered every 1–2 h, is as effective as the use of intravenous regular human insulin among patients with uncomplicated mild-to-moderate DKA. After an initial bolus subcutaneous dose of 0.2–0.3 U/kg, the administration of lispro or aspart (subcutaneous doses of 0.1 U/kg/h or 0.2 U/kg/2h) elicits a similar decline in glucose concentration as those

Box 1 | Treatment of hyperglycaemic crises

Intravenous fluids

1000–2000 ml 0.9% NaCl over 1–2 h for prompt recovery of hypotension and/or hypoperfusion. Switch to 0.9% saline or 0.45% saline at 250–500 ml/h depending upon serum sodium concentration. When plasma glucose level $\sim$ 11.1 mmol, change to dextrose in 5% saline.

Insulin

Regular human insulin intravenous bolus of 0.1 U/kg followed by continuous insulin infusion at 0.1 U/kg/h. When glucose level $\leq$ 13.9 mmol/l, reduce insulin rate to 0.05 U/kg/h. Thereafter, adjust rate to maintain glucose level $\sim$ 11.1 mmol/l. Subcutaneous rapid-acting insulin analogues might be an alternative to intravenous insulin in patients with mild-to-moderate DKA.

Potassium

Serum potassium level $>$ 5.0 mmol/l (no supplement is required); 4–5 mmol/l (add 20 mmol potassium chloride to replacement fluid); 3–4 mmol/l (add 40 mmol to replacement fluid); $<$ 3 mmol/l (add 10–20 mmol/h per hour until serum potassium level $>$ 3 mmol/l, then add 40 mmol to replacement fluid).

Bicarbonate

Not routinely recommended. If pH $<$ 6.9, consider 50 mmol/l in 500 ml of 0.45% saline over 1 h until pH increases to $\geq$ 7.0. Do not give bicarbonate if pH $\geq$ 7.0.

Laboratory evaluation

Initial evaluation should include blood count; plasma glucose; serum electrolytes, urea nitrogen, creatinine, serum or urine ketone bodies, osmolality; venous or arterial pH; and urinalysis. During therapy, measure capillary glucose every 1–2 h. Measure serum electrolytes, blood glucose, urea nitrogen, creatinine and venous pH every 4 h.

Transition to subcutaneous insulin

Continue insulin infusion until resolution of ketoacidosis. To prevent recurrence of ketoacidosis or rebound hyperglycaemia, continue intravenous insulin for 2–4 h after subcutaneous insulin is given. For patients treated with insulin before admission, restart previous insulin regimen and adjust dosage as needed. For patients with newly diagnosed diabetes mellitus, start total daily insulin dose at 0.6 U/kg/day. Consider multi-dose insulin given as basal and prandial regimen.

achieved using the intravenous route. Once glucose levels reach $\sim$ 13.8 mmol/l, the dose of subcutaneous insulin should be reduced by half and continued at the same interval until DKA resolves. Intramuscular administration of insulin is also effective in the treatment of DKA^{41,47}; however, this route tends to be more painful than subcutaneous injection and might increase the risk of bleeding among patients receiving anticoagulation therapy. The use of rapid-acting subcutaneous insulin analogues is not recommended for patients with severe hypotension or those with severe DKA or HHS. No prospective randomized studies have yet compared the subcutaneous infusion of rapid-acting insulin analogues with the intravenous infusion of regular human insulin among patients admitted to the ICU.

Potassium. Patients with DKA and HHS have a total-body potassium deficit of $\sim$ 3–5 mmol/kg⁴⁸. Despite this deficit, the serum potassium level measured on hospital admission is frequently within the normal range or even elevated owing to the shift of intracellular potassium to the extracellular compartment in the setting of hypertonicity, insulin deficiency and acidosis. Insulin therapy lowers serum potassium levels by promoting the movement of potassium back into the intracellular compartment. Potassium replacement should, therefore, be started when the serum concentration is $<$ 5.0 mmol/l to maintain a level of

4–5 mmol/l¹ (FIG. 1). The administration of 20–40 mmol of potassium per litre of fluids is sufficient for most patients; however, lower doses are required for patients with acute or chronic renal failure. Among patients with serum potassium levels $<$ 3.3 mmol/l, replacement should begin at a rate of 10–20 mmol/h and insulin therapy should be delayed until the potassium level rises above 3.3 mmol/l to prevent worsening of hypokalaemia¹.

Bicarbonate. Bicarbonate infusion is rarely required in the management of DKA. Indeed, the results of a systematic review of 12 randomized clinical studies on the efficacy of bicarbonate therapy in the treatment of severe acidemia in DKA reported that administration of bicarbonate offers no advantage in improving either outcome or the rate of recovery of hyperglycaemia and ketoacidosis⁴⁹. Bicarbonate therapy also has the potential to increase the risk of hypokalaemia and cerebral oedema¹. Nevertheless, clinical guidelines recommend the administration of 50–100 mmol of sodium bicarbonate as an isotonic solution (in 200 ml of water) among patients with a venous pH of $\leq$ 6.9 (REF. 1). Patients with DKA and a venous pH $>$ 7.0 and patients with HHS should not receive bicarbonate therapy.

Phosphate. Phosphate repletion is almost never required in the management of DKA as mild degrees of hypophosphataemia usually self-correct once the patient has resumed eating. The need for repletion is limited to patients with evidence of respiratory or cardiac distress who have serum phosphate levels $<$ 0.32 mmol/l. Studies have failed to show any beneficial effect of phosphate replacement on clinical outcome^{50,51}. Furthermore, aggressive phosphate therapy can be potentially hazardous, as indicated in case reports of children with DKA who developed hypocalcaemia secondary to intravenous phosphate administration^{52,53}.

Management after resolution of DKA and HHS

Criteria for resolution of DKA include a plasma glucose level $<$ 13.8 mmol/l, serum bicarbonate level $\geq$ 18 mmol/l, normalization of the anion gap and venous or arterial pH $\geq$ 7.3 (REFS 1, 14). The resolution of HHS is indicated by an effective serum osmolality $<$ 310 mmol/kg and a plasma glucose level $\leq$ 13.8 mmol/l in a patient who has recovered mental alertness^{1,14}.

The half-life of intravenous regular human insulin is $<$ 10 min; if the infusion is interrupted suddenly, patients might be at risk of ketoacidosis relapse and/or rebound hyperglycaemia. Therefore, insulin infusion should be continued for 2–4 h after subcutaneous insulin is started. Transition to subcutaneous insulin should be considered when the patient is alert and able to tolerate food by mouth. Patients with confirmed diabetes mellitus who were treated with subcutaneous insulin before hospital admission can resume their previous insulin regimen. Newly diagnosed patients or adult patients who have not previously received insulin can be started at a total dose of 0.5–0.7 U/kg/d¹. The use of a basal bolus regimen with insulin analogues is preferred over the use of intermediate-acting insulin (neutral protamine Hagedorn; NPH) and

regular human insulin^{1,54}. A randomized study compared the safety and efficacy of insulin analogues and regular human insulin during the transition from intravenous to subcutaneous administration among patients with DKA⁴². No differences were detected in mean daily glucose levels; however, 41% of patients treated with NPH or regular human insulin had an increased rate of hypoglycaemia versus 15% in those treated with once-daily glargine or glulisine before meals.

To avoid rebound hyperglycaemia following acute management of DKA, one study administered the long-acting insulin analogue glargine at a dose of 0.25 U/kg within 12 h of initiation of intravenous insulin infusions. The incidence of rebound hyperglycaemia was lower in the group receiving glargine than in the control group (no glargine; 94% versus 33%; $P < 0.001$) and there was no increased risk of hypoglycaemia among patients who received the insulin analogue⁵⁵.

Prevention of hyperglycaemic crises

Many cases of DKA can be avoided by improved outpatient treatment and follow-up programmes, as well as by the implementation of initiatives to engage patients with diabetes mellitus in self-management education and adherence to self-care^{56,57}.

The frequency of hospitalizations for DKA was reduced following diabetes education programmes, improved follow-up care and access to medical advice⁵⁸. Patients should be instructed on how to adjust their insulin dosage during illness, emphasizing that insulin should never be discontinued. Patients also need to be informed on how to contact their healthcare providers and how to maintain adequate fluid intake in the setting of hyperglycaemia¹⁴. Providing patients with T1DM with instructions on the use of home monitoring of blood ketone body levels during illness and the management of persistent hyperglycaemia could enable early recognition of impending ketoacidosis.

The FDA and European Medicines Agency have both issued statements warning that treatment with SGLT2 inhibitors might be associated with an increased risk of DKA^{59,60}. The exact prevalence of DKA among patients receiving these drugs is unknown but SGLT2 inhibitors seem to primarily affect individuals with T1DM^{25,61}. The estimated incidence of DKA among patients with T2DM who are receiving various SGLT2 inhibitors is 0.1–0.8 per 1,000 patient-years⁶¹. Most cases of DKA occur among patients with a concomitant precipitating cause (for example, surgery, alcohol abuse, insulin-pump malfunction and poor adherence to insulin treatment)^{25,61}. Increased awareness among healthcare professionals, as well as patient education, might facilitate early detection of DKA during SGLT2-inhibitor treatment or even prevent development of this diabetic emergency. Potential strategies include routine monitoring of blood and urine ketone bodies during acute illness, periods of starvation, and in the presence of hyperglycaemia. Until more information is available, the use of SGLT2 inhibitors should be avoided during severe illness, major surgical procedures and when ketone bodies are detected despite increases in insulin dose.

Hypoglycaemia

Hypoglycaemia is the most frequent and serious adverse effect of antidiabetic therapy. This complication represents a major barrier to achieving desired levels of glycaemic control in both outpatient and inpatient settings⁶².

Precipitating causes

Severe hypoglycaemia occurs in ~30–40% of patients with T1DM and ~10–30% of patients with insulin-treated T2DM each year^{63–66}. Numerous patients experience more than one hypoglycaemic event annually. The frequency of mild hypoglycaemia is difficult to quantify as many of these events go unreported because the affected individual quickly treats them. In a study based on self-report, 216 of 418 (51%) patients with T1DM or T2DM who responded to a questionnaire reported experiencing a mild hypoglycaemic event in the past year⁶⁷. The investigators did not describe these mild events owing to concerns that some represented anxiety about hypoglycaemia rather than a true hypoglycaemic event. When given the definition for severe hypoglycaemia as 'events requiring third-party assistance,' 26 of 92 (28%) patients with T1DM and 55 of 326 (17%) patients with T2DM reported experiencing one or more events in the past year⁶⁷. Although this study had the limitations associated with self-reported survey data, the estimates are consistent with other reports^{64,65}.

A study that analysed data from two large national surveys found that hypoglycaemia accounted for more than 97,000 visits to the emergency room each year, one-third of which required hospitalization⁵. Insulin therapy and insulin secretagogues were identified as the medications most frequently associated with hypoglycaemia. Sulfonylureas and insulin were reported as the agents most frequently associated with emergency room admissions, particularly among patients aged >80 years. This subgroup was fivefold more likely to require hospitalization than patients aged <80 years.

In a study of patients with T1DM or T2DM who were hospitalized at one of 29 academic medical centres, 12–18% of all admissions were associated with at least one episode of hypoglycaemia, defined as a glucose value <3.3 mmol/l⁶⁸. Severe hypoglycaemia, defined as a glucose value <2.2 mmol/l, occurred in <5% of admissions^{7,68,69}. A study comparing glycaemic data among ICU patients in the pre-NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) versus the post-NICE-SUGAR trial era observed that 7.2% and 5.9% of patient-days were associated with glucose values <3.9 mmol/l, and 0.9% and 0.7% with values <2.2 mmol/l, respectively⁷⁰.

In the hospital setting, hypoglycaemia can occur among patients with or without a history of diabetes mellitus, as well as among those who either are or are not receiving glucose-lowering therapies. Spontaneous hypoglycaemia has been defined as events that occur in the absence of any glucose-lowering therapies. This complication might be observed among patients with dementia, severe illness, sepsis, end-stage renal disease, cancer, or liver disease, and serves as an indicator of illness severity and mortality risk^{16,17}.

Box 2 | Factors contributing to hypoglycaemia

- Insufficient patient education
- Medications (insulin, sulfonylureas, glinides, quinolones)
- Aggressive treatment protocols targeting normoglycaemia
- Poor coordination of insulin administration and food delivery
- Abrupt changes in nutritional intake
- Abrupt discontinuation of parenteral or enteral nutrition among insulin-treated patients
- Decline in renal or hepatic function
- Severe illness
- Tapering of steroid doses without appropriate reductions in insulin
- Inappropriate insulin dosing
- Counter-regulatory hormone deficiencies
- Impaired awareness of hypoglycaemia
- Dementia
- Age >65 years
- Sepsis

Contributing factors to iatrogenic hypoglycaemia include age >65 years, underlying renal or hepatic insufficiency, long duration of diabetes mellitus, presence of other diabetic complications, intensive glycaemic control, counter-regulatory hormone deficiencies, variability in food intake, errors in insulin dosing, and a history of hypoglycaemia events^{5,21,71} (BOX 2). In the hospital setting, use of correction insulin for bedtime hyperglycaemia contributes to the risk of overnight hypoglycaemia⁷².

Diagnosis

Several different glycaemic values have been used to define hypoglycaemia in inpatient and outpatient settings; however, the definition used by the American Diabetes Association and the Endocrine Society is any plasma glucose level <3.9 mmol/l⁷³. This value is approximately equivalent to the lower limit of the normal range for postabsorptive plasma glucose concentrations and represents the glycaemic threshold for activation of glucose counter-regulatory systems among nondiabetic individuals^{74,75}. This definition also encompasses published values that use venous, capillary or interstitial glucose levels and so provides a margin of safety when blood glucose levels are measured with home glucose metres or continuous glucose monitoring devices, which have variable correlation with laboratory glucose values.

Mild hypoglycaemia is defined as any plasma glucose level ≤ 3.9 mmol/l that can be self-treated. The occurrence of a mild hypoglycaemic event does not usually require a visit to the emergency room; however, recurrent mild hypoglycaemic events increase the risk of severe hypoglycaemia, which is defined as the need for assistance from another person to take corrective action⁷³. Severe hypoglycaemic events account for the majority of visits to the emergency room and subsequent hospital admissions⁵. Impaired awareness of hypoglycaemia refers to the reduced ability of the affected

individual to recognize a decline in glucose levels before the onset of neuroglycopenic symptoms^{20,62,64,75}. In the hospital setting, severe hypoglycaemia has been defined as any plasma glucose level <2.2 mmol/l, independent of altered sensorium^{76–78}. The rationale for the different definitions of severe hypoglycaemia in the inpatient setting reflects the fact that hospitalized patients might have an impaired ability to detect or report usual hypoglycaemic symptoms.

Adverse effects

Hypoglycaemia is associated with both immediate and delayed adverse clinical outcomes^{20–22}. Acute adverse outcomes include seizures, arrhythmias, alterations in the level of consciousness and cardiovascular events (myocardial infarction and stroke)^{20,62,79–81}. Severe outcomes, such as brain damage and death, have also been observed, usually in the setting of unrecognized severe hypoglycaemia of long duration^{13,62,82–84}. Similar to what is observed with hyperglycaemia, hypoglycaemia increases levels of pro-inflammatory cytokines, markers of lipid peroxidation, reactive oxygen species and leukocytosis⁸⁵. Recurrent episodes of severe hypoglycaemia can increase risk of cardiovascular disease and death^{81,86,87}.

Questions regarding the contribution of hypoglycaemia to adverse cardiovascular outcomes were raised following publication of large clinical trials that demonstrated no reductions in cardiovascular disease events among intensively treated patients with T2DM^{88–91}. In each of these studies, the occurrence of severe hypoglycaemia was more frequent among the intensively treated participants (twofold to threefold) than the conventionally treated participants, a situation that might have hampered the ability to recognize any benefit of improved levels of glycaemic control. Severe hypoglycaemia was associated not only with an increased incidence of macrovascular events and deaths from cardiovascular disease but also with microvascular events and non-cardiovascular mortality⁹⁰. Whether these adverse outcomes were a direct result of hypoglycaemia, or a marker of underlying vulnerability, has not been established.

In one study, a group of patients with T2DM who either had concomitant cardiovascular disease or who were at high risk of cardiovascular disease were assessed using continuous electrocardiography Holter monitoring in conjunction with a continuous glucose monitoring system able to detect hypoglycaemia to a level of 1.1 mmol/l⁸⁰. Nocturnal hypoglycaemia was associated with lower glucose values, which persisted for a longer duration, than those observed with daytime hypoglycaemia. Bradycardia, atrial arrhythmia and ventricular ectopy were more prevalent during nocturnal (but not daytime) hypoglycaemia when compared with euglycaemia. Both daytime and nocturnal hypoglycaemia were associated with increased ventricular ectopy, which manifested primarily as an increase in ventricular premature beats, with a greater increase occurring during nocturnal episodes⁸⁰ (FIG. 2). These cardiac abnormalities are similar to those observed among patients with T1DM during hypoglycaemia⁹². Hyperglycaemia (defined as a glucose level ≥ 15 mmol/l)

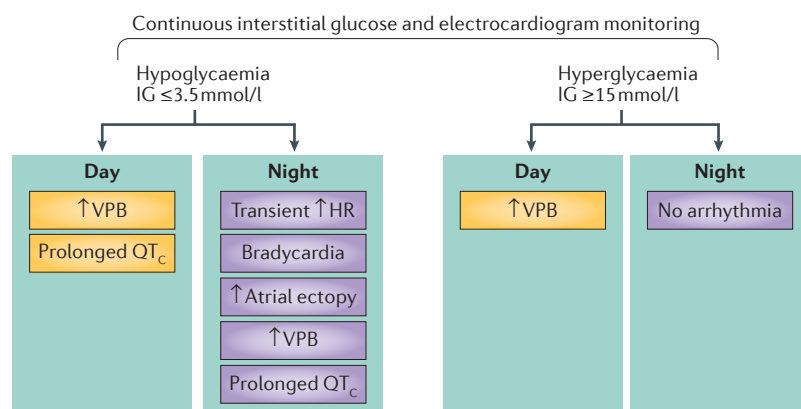


Figure 2 | Differential effects of daytime versus night time hypoglycaemia on cardiovascular risk. Nocturnal hypoglycaemia is associated with more cardiac arrhythmias than what is observed during daytime hypoglycaemia. Hyperglycaemia was associated with an increased risk for VPB during the day but not overnight. HR, heart rate; IG, interstitial glucose; QT_c, cardiac repolarization interval; VPB, ventricular premature beats.

was not associated with atrial arrhythmias or complex ventricular arrhythmias at any time of the day; however, the risk of ventricular arrhythmias was similar to that observed with daytime hypoglycaemia⁸⁰.

Blood pressure elevations (>180/120 mm Hg), hypokalaemia and prolonged QT intervals on electrocardiography, were observed in a study of 414 visits to an emergency department for severe hypoglycaemia (defined as the inability of the patient to self-treat)⁸³. Mean nadir plasma glucose levels were similar among the 88 patients with T1DM and the 326 with T2DM (1.8 and 1.7 mmol/l, respectively); however, cardiovascular disease events and death were observed only in the population with T2DM.

Together, the findings of these studies provide evidence that hypoglycaemia contributes to cardiovascular morbidity and mortality through several potential mechanisms, such as increased sympathetic nervous system activation, catecholamine excess and abnormal cardiac repolarization with the development of atrial and cardiac arrhythmias^{91,93}. Other proposed mechanisms include increased thrombogenesis, inflammation, vasoconstriction and impaired cardiac autonomic function, all of which can contribute to ischaemia among susceptible individuals^{91,93}.

The occurrence of hypoglycaemic events in the inpatient setting has also been associated with adverse outcomes. Several studies have reported that spontaneous, but not insulin-mediated or iatrogenic, hypoglycaemia contributes to morbidity and mortality among hospitalized patients^{16,17}. By contrast, other studies have reported that insulin-mediated hypoglycaemia is associated with increased morbidity and mortality^{18,19,62}. In one study, insulin-treated patients experiencing hypoglycaemia (glucose levels <2.8 mmol/l) had a lower death rate than patients with spontaneous hypoglycaemia but a higher death rate than those receiving insulin without a hypoglycaemic event¹⁸. In the NICE-SUGAR study¹⁹, moderate and severe hypoglycaemias were associated

with increased risk of death, although a definitive cause-and-effect relationship could not be established. In one retrospective cohort study of >4,000 patients with confirmed diabetes mellitus who were admitted to general medical wards, both early mortality (in hospital) and late mortality (at 1 year after discharge) were higher among patients who had experienced at least one hypoglycaemic episode than those who had not²².

Hypoglycaemic events exert adverse consequences other than increasing cardiovascular morbidity and mortality. Deterioration in cognitive function, increased risk of falls, decreased health-related quality of life, increased absenteeism from work, decreased work productivity and fear of hypoglycaemia have all been reported with deterioration in overall glycaemic control^{67,94,95}.

Management

Clinicians must provide patients and their family with information on how to recognize and treat both mild and severe hypoglycaemic events when they occur.

In both outpatient and inpatient settings, mild hypoglycaemic events can be treated by oral administration of rapidly absorbed carbohydrate, glucose tablets or glucose gel (BOX 3). Mild events can be readily treated in the outpatient setting using the so-called 'rule of 15'. This rule recommends consuming 15 g of carbohydrate; allowing 15 min for absorption of nutrients and return of plasma glucose to levels within the normal range; and repeating glucose measurement after another 15 min. Some hypoglycaemic episodes can require ≥30 g of carbohydrate to restore normoglycaemia. In the inpatient setting, the introduction of nurse-directed hypoglycaemia treatment protocols guide oral administration of 15–30 g of rapidly absorbed carbohydrate for the immediate treatment of any glucose level <3.9 mmol/l^{96,97}. Some institutions have incorporated hypoglycaemic treatment regimens into computerized or standardized order sets that guide the prescribing of scheduled basal, bolus and correction insulin therapy^{98–101}.

Severe hypoglycaemic events that are associated with changes in the level of consciousness require third-party assistance. All insulin-treated patients should, therefore, be provided with a glucagon kit and their family members, friends and co-workers educated in its use in the event of severe hypoglycaemia.

In the inpatient setting, severe hypoglycaemic episodes among patients who are either not awake or unable to ingest oral nutrition require the administration of intravenous solutions that contain dextrose. The specific dose of oral or intravenous glucose administration required to resolve hypoglycaemia while avoiding rebound hyperglycaemia is not clearly defined. In one study, 54 patients experiencing hypoglycaemia associated with a decline in mental status were randomly assigned to receive a 10% or 25% solution of dextrose, administered in 5 g aliquots of 50 ml or 5 ml, respectively. Doses were repeated at 1-min intervals until the patient either regained consciousness or the maximum dose of 25 g was administered. Despite similar pre-treatment glucose levels, the group receiving the 10% dextrose solution required a median total dose of 10 g,

Box 3 | Prevention of hypoglycaemia in hospitalized patients

- Use of rational goal-directed insulin therapy with weight-based dosing strategies
- Modification of insulin dosing for glucose values <5.5 mmol/l
- Administration of dextrose-containing solutions in the event of unanticipated discontinuation of enteral or parenteral nutrition among insulin-treated patients
- Modification of bedtime correction insulin dosing
- Avoid use of sulfonylureas among high-risk patients (age >65 years; estimated glomerular filtration rate <45 ml/min; those receiving basal insulin)

whereas the group receiving the 25% dextrose solution required a dose of 25 g¹⁰². No between-group differences were observed in the time to resolution of mental status changes (8 min); however, post-treatment glucose levels were lowest among patients receiving the 10% dextrose solution.

Subcutaneous or intramuscular administration of glucagon (1 mg) provides an effective option for treatment in cases where intravenous access is not immediately available (for example, patients who are mentally obtunded or unable to take oral supplementation). However, glucagon therapy is not recommended for glycogen-depleted patients, such as those with heavy alcohol use or following high levels of exercise (for example, after completing a marathon race)¹⁰³. Questions have been raised regarding the need to pretreat patients with a history of heavy alcohol use or severe nutritional deficiencies with thiamine before intravenous administration of glucose. This recommendation is based on concern for precipitating Wernicke encephalopathy, a neurological disorder associated with delirium, oculomotor dysfunction and ataxia that can be iatrogenically precipitated by glucose loading among patients with thiamine deficiency¹⁰⁴. In the setting of hypoglycaemia, correction of blood glucose is recommended as the initial treatment, followed by early administration of intravenous thiamine among patients suspected as being at risk of Wernicke encephalopathy¹⁰⁴.

Sulfonylurea-associated hypoglycaemia can be prolonged and severe, particularly among patients with underlying renal insufficiency¹⁰⁵. Use of oral and parenteral glucose administration has the potential to aggravate hypoglycaemia among patients with sulfonylurea-associated hypoglycaemia as these drugs mediate glucose-stimulated insulin secretion. Use of short-acting octreotide (50–75 µg administered subcutaneously or intravenously) can inhibit insulin secretion acutely, which negates the need for repeated doses of oral or intravenous glucose while waiting for the effects of the sulfonylurea to dissipate¹⁰⁶.

Prevention

Most hypoglycaemic episodes can be either prevented or limited to mild events. All patients treated with insulin or an insulin secretagogue in the outpatient setting require education about the risk, symptoms and treatment of hypoglycaemia¹⁰⁷ (BOX 3). Educational interventions that focus on glucose-awareness training have substantially reduced the frequency and severity of hypoglycaemic events, often without any deterioration in glycaemic control^{74,75,108,109}.

Among patients with severe hypoglycaemia owing to impaired awareness, implementation of glycaemic goals that scrupulously target avoidance of low blood glucose levels can help restore hypoglycaemia awareness and so reduce the risk of future events^{64,110,111}. A meta-analysis of studies that targeted interventions to restore awareness of hypoglycaemia symptoms and so reduce risk of severe hypoglycaemia among patients with T1DM concluded that patient education programmes in concert with avoidance of intensive glycaemic targets might be an effective approach¹¹¹.

Modification of pharmacological strategies for glycaemic control can also effectively reduce the frequency and severity of hypoglycaemic events. Among insulin-treated patients with either T1DM or T2DM, switching to long-acting or short-acting insulin analogues can reduce the risk of hypoglycaemic events¹¹¹. Although insulin analogues are more expensive than regular human insulin preparations, they are particularly useful among patients identified at high risk of hypoglycaemia^{74,112}. For patients already using insulin-analogue therapy, continuous subcutaneous insulin infusions, provided either alone or in combination with continuous glucose monitoring devices, can reduce hypoglycaemia risk¹¹³.

For inpatients with diabetes mellitus or newly recognized hyperglycaemia who are receiving glucose-lowering therapies, glycaemic targets have been modified from earlier recommendations of 4.4–6.1 mmol/l to 5.5–10.0 mmol/l. This range avoids the adverse effects of uncontrolled hyperglycaemia while minimizing the risk of hypoglycaemia^{76–78}. Modification of glucose-lowering medications is recommended when the plasma glucose level declines to <5.5 mmol/l^{76–78}. Weight-based insulin dosing strategies using 0.4–0.5 U/kg/day as a total daily dose for basal bolus or 0.20–0.25 U/kg/day for basal plus insulin regimens have been demonstrated to improve glycaemic control among hospitalized patients with T2DM when compared to sliding scale insulin regimens, but also increase the percentage of patients experiencing hypoglycaemia^{76,99}. Reducing the total insulin dose to 0.1–0.2 U/kg/day is preferable for patients at increased risk of hypoglycaemia¹¹⁴. These patients include individuals with lean body habitus, age >65 years, renal or hepatic insufficiency, or a history of severe hypoglycaemic events. In one study, patients with T2DM and a low estimated glomerular filtration rate were randomly assigned to basal bolus insulin therapy with either glargine or glulisine (0.25 or 0.50 U/kg/day)¹¹⁴. The incidence of hypoglycaemia among patients receiving the 0.25 U/kg/day dose was approximately half of that seen with the higher dose, without causing additional hyperglycaemic episodes.

Conclusions

DKA, HHS and hypoglycaemia are commonly encountered medical emergencies among patients with diabetes mellitus. DKA and HHS are most likely to develop in the outpatient setting, prompting hospital admission, whereas hypoglycaemia is a frequent complication of glucose-lowering therapy in both outpatient and inpatient settings. For patients with DKA and HHS, appropriate administration of intravenous fluids and

insulin, with attention to associated fluid and electrolyte disorders, can effectively and rapidly resolve the metabolic dysregulation. Hypoglycaemia also requires immediate recognition and aggressive management. Tailoring glycaemic goals and individualizing glucose-lowering therapies according to age, presence of comorbidities and individual risk of hypoglycaemia, can also contribute to a lowered risk of severe hypoglycaemic events. In the hospital, nurse-directed

hypoglycaemia treatment protocols that guide immediate therapy before notifying the treating physician can effectively offset deterioration of a mild hypoglycaemic event to a severe episode with associated adverse sequelae. Following acute management and restoration of physiological glucose levels, DKA, HHS and hypoglycaemia all require identification of the precipitating cause to prevent these potentially life-threatening diabetic complications from recurring.

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Author contributions

G.U. and M.K. researched data for the article, made substantial contributions to discussions about the content, wrote the article and reviewed and/or edited the manuscript before submission.

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G.U. declares that he has received consulting fees or/and honoraria for membership of advisory boards from Boehringer Ingelheim, Glytec, Johnson and Johnson, Merck, Novo Nordisk and Sanofi, and that he has received unrestricted research support for inpatient studies (to Emory University School of Medicine) from Astra Zeneca, Boehringer Ingelheim, Merck, Novo Nordisk and Sanofi. M.K. declares no competing interests.

Review criteria

References were identified by searching the OVID MEDLINE and PubMed databases (1946–2015) using the terms “type 1 diabetes”, “type 2 diabetes”, “diabetic ketoacidosis”, “hyperglycaemia”, “hypoglycaemia”, “inpatient” and “sulfonylureas”. English-language full-text manuscripts were selected whenever possible. References were also identified through review of manuscripts selected using the search engines described above, in addition to use of the “Similar articles” and “Cited by” sidebars provided by PubMed. Several of the references were suggested by peer reviewers.