Management of Hyperglycemic Crises

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Maya Fayfman, MD, Francisco J. Pasquel, MD, MPH, Guillermo E. Umpierrez, MD, CDE*

KEYWORDS

- Hyperglycemic emergencies • Diabetic ketoacidosis
- Hyperglycemic hyperosmolar state • Management of hyperglycemic emergencies
- Diabetes

KEY POINTS

- Hyperglycemic emergencies are life-threatening complications of diabetes.
- This article reviews diabetic ketoacidosis and hyperglycemic hyperosmolar state addressing historical context, epidemiology, clinical features, and guidelines for management.

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the most serious and life-threatening hyperglycemic emergencies in patients with diabetes. Although DKA and HHS are often discussed as separate entities, they represent points along a spectrum of hyperglycemic emergencies owing to poorly controlled diabetes. Both DKA and HHS can occur in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D); however, DKA is more common in young people with T1D and HHS is more frequently reported in adult and elderly patients with T2D. In many patients, features of the 2 disorders with ketoacidosis and hyperosmolality may also coexist. The frequency of DKA has increased by 30% during the past decade, with more than 140,000 hospital admissions per year in the United States.[1,2] The rate of hospital admissions for HHS is lower than for DKA, accounting for less than 1% of all diabetes-related admissions.[3,4] Both disorders are characterized by insulinopenia

Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, 69 Jesse Hill Jr. Drive Southeast, 2nd Floor, Atlanta, GA 30303, USA
* Corresponding author. Emory University School of Medicine, 49 Jesse Hill Jr. Drive Southeast, 2nd Floor, Atlanta, GA 30303.
E-mail address: Geumpie@emory.edu

Med Clin N Am 101 (2017) 587–606
http://dx.doi.org/10.1016/j.mcna.2016.12.011 **medical.theclinics.com**

and severe hyperglycemia. Early diagnosis and management are paramount to improve patient outcomes. The mainstays of treatment in both DKA and HHS are aggressive rehydration, insulin therapy, electrolyte replacement, and discovery and treatment of underlying precipitating events. Herein we review the epidemiology, pathogenesis, diagnosis, and provide practical recommendations for the management of patients with hyperglycemic emergencies.

HISTORICAL REVIEW OF DIABETIC COMAS

The first detailed clinical description of diabetic coma in an adult patient with severe polydipsia, polyuria, and a large amount of glucose in the urine followed by progressive decline in mental status and death was reported by August W. von Stosch in 1828.[5] This publication was followed by several case reports describing young and adult patients with newly diagnosed or with established diabetes who presented with an abrupt clinical course of excessive polyuria, glycosuria, coma, and death.[6–8] In 1874, The German physician Adolf Kussmaul reported that many cases of diabetic coma were preceded by deep and frequent respiration and severe dyspnea.[9,10] Kussmaul breathing rapidly became one of the hallmarks of diabetic coma. Shortly after that, it was reported that in many of these patients, the urine contained large amounts of acetoacetic acid and β-hydroxybutyric acid.[11,12] Dr Julius Dreshfeld in 1886 was the first to provide a comprehensive description of the 2 different categories of diabetic coma,[13] one with Kussmaul breathing and positive ketones and the other, an unusual type of diabetic coma in older, well-nourished individuals, characterized by severe hyperglycemia and glycosuria but without Kussmaul breathing, fruity breath odor, or a positive urine acetone test.

Before the discovery of insulin in 1921, the mortality rate of patients with DKA was greater than 90%. The first successful case of DKA treated with insulin was reported by Banting and associates[14] in a 14-year-old boy who presented with a blood glucose of 580 mg/dL and strongly positive urinary ketones at the Toronto General Hospital in 1923. These authors reported a dramatic improvement in glycosuria along with disappearance of acetone bodies in the urine after a few doses of pancreatic extract injections.[14] After the discovery of insulin, the mortality rate associated with diabetic comas decreased dramatically to 60% in 1923 and 25% by the 1930s,[15] 7% to 10% in the 1970s[16,17] and is currently less than 2% in patients for DKA[1,18,19] and between 5% and 16% in patients with HHS.[20,21]

EPIDEMIOLOGY

Although DKA occurs more commonly in patients with autoimmune T1D, the cumulative number of cases of DKA reported in patients with T2D represents at least one-third of all cases.[22] Global epidemiologic studies have reported on the incidence of DKA among patients with T1D. An analysis from the Prospective Diabetes Registry in Germany including 31,330 patients reported a DKA admission rate of 4.81 per 100 patient-years (95% confidence interval [CI], 4.51–5.14).[23] Individuals with the highest risk included those with high hemoglobin A1c (HbA1c), longer diabetes duration, adolescents, and girls.[23] Multinational data from 49,859 children (<18 years) with T1D across 3 registries and 5 nations similarly found higher odds of DKA among females (odds ratio [OR], 1.23; 99% CI, 1.10–1.37), ethnic minorities (OR, 1.27; 99% CI, 1.11–1.44), and among those with an HbA1c of 7.5% or greater (OR, 2.54 [99% CI, 2.09–3.09] for an HbA1c from 7.5 to <9% and OR 8.74 [99% CI, 7.18–10.63] for an HbA1c of ≥9.0%).[24] Data from the T1D Exchange Clinic Network including 2561 patients, shows that young adults (18–25 years) have the highest occurrence of

DKA (approximately 5%) defined as 1 or more events in the prior 3 months.[25] HHS typically occurs in older patients with T2D[20]; however, it is being recognized as an emerging problem in children and young adults.[26]

Similar mortality rates have been reported in European countries, but the reported mortality continues to be higher than 10% in Indonesia and sub-Saharan African countries.[27,28] HHS occurs most commonly in older patients with T2D with an intercurrent illness such as an infection, surgery, or ischemic events, and is associated with a higher mortality rate than DKA. Mortality in patients with HHS is reported between 5% and 16%, which is about 10 times higher than the mortality in patients with DKA.[20,21,29] The cause of death in patients with DKA and HHS rarely results from the metabolic complications of hyperglycemia or metabolic acidosis, but relates to the underlying precipitating cause, severity of dehydration, and advanced age.[1,4,30]

Treatment of patients with DKA and HHS is associated with substantial mortality and health care costs. DKA is the leading cause of mortality among children and young adults with T1D, accounting for approximately 50% of all deaths in diabetic patients younger than 24 years of age.[1] In the United States, the overall inpatient DKA mortality is less than 1%,[1,2] but a higher rate is reported among elderly patients with life-threatening illnesses.[1,2,31,32] Similar mortality rates have been reported in European countries, but the reported mortality continues to be higher than 10% in countries with limited acute care resources.[28] A history of recurrent DKA episodes increases substantially the long-term mortality after discharge, particularly among young, socially disadvantaged adults with very high HbA1c.[33] In a retrospective review from the United Kingdom, the long-term mortality after a single episode of DKA was 5.2% (4.1 years of follow-up [range, 2.8–6.0]) compared with 23.4% in those with recurrent DKA admissions (2.4 years of follow-up [range, 2.0–3.8]; hazard ratio, 6.18).[33]

Inpatient mortality has been reported in 5% to 16% of patients with HHS, a rate that is approximately 10-fold higher than that reported for DKA.[20,21,29] The prognosis and outcome of patients with HHS is determined by the severity of dehydration, presence of comorbidities and advanced age. In addition, patients with a history of HHS are at significant risk of mortality after hospitalization, in particular those with multiple episodes. Compared with patients with diabetes without HHS, a recent study reported that, after adjustment for age, sex, selected comorbidities, and monthly income, the mortality hazard ratio was 2.8 and 4.5 times higher in subjects with one episode and 2 or more episodes of hyperglycemic crisis, respectively.[34] National data shows a decrease in deaths related to both hyperglycemic crises with an absolute decline of 529 deaths in the period of 1990 to 2010 (2.7 fewer cases per 10,000; 95% CI, 2.4–3.0).[35]

Treatment of hyperglycemic crises represents a substantial economic burden, with an estimated total annual hospital cost of $2.4 billion.[1] In the United States, it is estimated that DKA episodes represent more than $1 of every $4 spent on direct medical care for adult patients with T1D and $1 of every $2 in those patients with multiple DKA episodes.[36]

PRECIPITATING CAUSE

The most common precipitating causes of DKA reported in different epidemiologic studies worldwide are shown in **Table 1**. DKA is the initial presentation of diabetes in approximately 15% to 20% of adults and in approximately 30% to 40% of children with T1D.[4,37,38] Infection is the most common cause of DKA around the world; however, poor adherence to insulin treatment is the most common precipitating cause

Table 1
Precipitating causes of diabetic ketoacidosis by country

Precipitating Causes, %	Australia	Brazil	China	Indonesia	Korea	Nigeria	Spain	Syria	Taiwan	USA
Newly diagnosed 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

Abbreviations: NA, not applicable; NR, not reported.

Adapted from Umpierrez G, Korytkowski M. Diabetic emergencies-ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12(4):223; with permission.

of DKA in young patients with T1D and in inner city populations in the United States.[39–41] According to a recent report from a safety net hospital in Atlanta, insulin discontinuation accounted for 56% of patients with their first and 78% of patients with multiple DKA episodes.[39] Other potential precipitants of DKA included infections (14%) and noninfectious illnesses (4%)[39] such as acute myocardial infarction, neurovascular accidents, alcohol use, and pancreatitis.[42] Psychological risk factors including depression and eating disorders have been reported in up to 20% of recurrent episodes of ketoacidosis in young patients.[39,43,44] Insulin pump malfunction has long been recognized as a cause of DKA[45,46] owing to the short-acting insulin formulation used in pumps; however, this is not a common event with newer, improved pump technology.[47,48]

Urinary tract infection and pneumonia are common precipitating causes of HHS,[46,49] as well as acute cardiovascular events and other concomitant medical illnesses.[20,50] Poor adherence to medical therapy and new diabetes onset are less common precipitating cause of HHS than DKA.[49]

Several medications that altered carbohydrate metabolism may precipitate the development of DKA and HHS, including glucocorticoids, beta-blockers, thiazide diuretics, certain chemotherapeutic agents,[50,51] and atypical antipsychotics.[52–55] One large retrospective review from the UK reported that hyperglycemic emergencies occurred at a rate of 1 to 2 per 1000 person-years after initiation of antipsychotics.[56] Of the antipsychotics, olanzapine and risperidone were associated with the greatest risk.[56]

Recently, the sodium glucose cotransporter 2 (SGLT-2) inhibitors, a new class of oral antidiabetic agents that lower plasma glucose by inhibiting proximal tubular reabsorption of glucose in the kidney, have been associated with DKA in patients with T1D and T2D.[57,58] An atypical presentation of DKA, which can lead to delayed recognition and treatment, has been referred to as "euglycemic DKA" owing to only mild to moderate elevations in blood glucose reported in many cases.[57] Compiled data from randomized studies with the use of SGLT-2 inhibitors reported a very low incidence of DKA in patients with T2D (approximately 0.07%[59,60]); however, the risk of ketosis and DKA is higher in patients with T1D. About 10% of patients with T1D treated with SGLT-2 inhibitors develop ketosis and 5% require hospital admission for DKA.[57] Potential mechanisms have been proposed, including higher glucagon levels, reduction of daily insulin requirement leading to a decrease in the suppression of lipolysis and ketogenesis, and decreased urinary excretion of ketones.[58,61]

PATHOPHYSIOLOGY

The 2 most important pathophysiologic mechanisms for DKA and HHS are significant insulin deficiency and increased concentration of counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (**Fig. 1**).[62–64] The insulin deficiency of DKA can be absolute in patients with T1D or relative as observed in patients with T2D in the presence of stress or intercurrent illness.[65] Insulin deficiency coupled with increased counterregulatory hormones lead to increased hepatic glucose production owing to increased hepatic gluconeogenesis and glycogenolysis,[66] as well as reduced glucose use in peripheral tissues, in particular muscle.[67] Insulinopenia also leads to activation of hormone-sensitive lipase and accelerated breakdown of triglycerides to free fatty acids (FFAs).[68] In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon[69,70] and increased glucagon/insulin ratio.[71] The increased glucagon/insulin ratio lowers the activity of malonyl coenzyme A, the enzyme that modulates movement of FFA into the hepatic mitochondria where

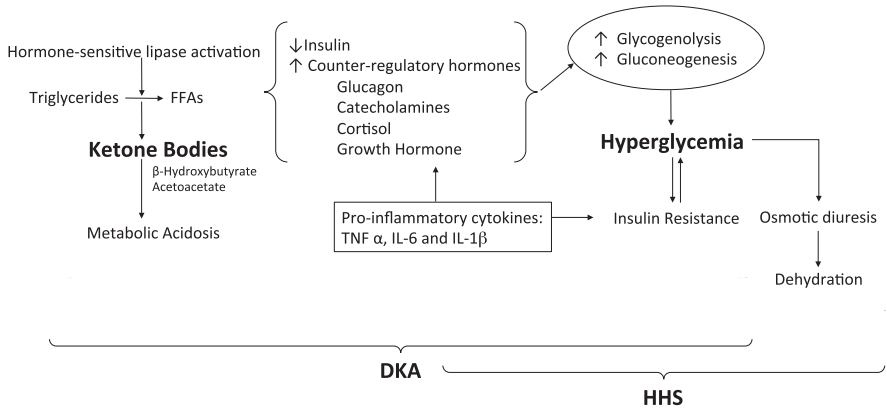

Fig. 1. Pathogenesis of hyperglycemic emergencies. Hyperglycemia and accumulation of ketones bodies result from a relative or absolute insulin deficiency and excess counterregulatory hormones (glucagon, cortisol, catecholamines, and growth hormone). Increased ketone bodies and diabetic ketoacidosis (DKA). Decrease in insulin levels combined with increase in counterregulatory hormones, particularly epinephrine causes the activation of hormone sensitive lipase in adipose tissue and breakdown of triglyceride into glycerol and FFAs. In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon. The 2 major ketone bodies are β-hydroxybutyrate and acetoacetic acid. Accumulation of ketone bodies leads to a decrease in serum bicarbonate concentration and metabolic acidosis. Higher insulin levels present in hyperglycemic hyperosmolar state (HHS) inhibit ketogenesis and limit metabolic acidosis. When insulin is deficient, hyperglycemia develops as a result of 3 processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose use by peripheral tissues. Hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate and worsening hyperglycemia. TNF, tumor necrosis factor.

fatty acid oxidation takes place. The increased production of ketone bodies (acetoacetate and β-hydroxybutyrate), 2 strong acids, leads to reduction of bicarbonate and metabolic acidosis.

Several mechanisms have been proposed to explain the absence or minimal presence of ketone bodies in patients with HHS including higher levels of circulating insulin, lower levels of counterregulatory hormones and FFAs, and inhibition of lipolysis by the hyperosmolar state (see **Fig. 1**). Of them, higher insulin secretion seems to be the most important mechanism to prevent ketosis in HHS compared to patients with DKA.[64] This is owing to the fact that the antilipolytic effect of insulin is about one-tenth that of glucose use.

Oxidative Stress and Inflammation

Several experimental and clinical studies have shown that the development of hyperglycemia and ketoacidosis result in an inflammatory state characterized by an elevation of proinflammatory cytokines and increased oxidative stress markers.[72,73] Severe hyperglycemia-induced macrophage production of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-6 and IL-1β, and C-reactive protein, which in turn lead to impaired insulin secretion as well as reduced insulin sensitivity.[73–75] Increases in FFAs also increases insulin resistance as well as impaired nitric oxide production in endothelial cells and endothelial dysfunction.[76] The increased inflammatory response, oxidative stress and generation of reactive oxygen species can

lead to capillary perturbation and cellular damage of lipids, membranes, proteins, and DNA.[73,77]

DIAGNOSIS OF DIABETIC KETOACIDOSIS

Signs and Symptoms

Patients with DKA often present following a short clinical course characterized by fatigue and classic symptoms of hyperglycemia: polyuria, polydipsia, and weight loss. Gastrointestinal complaints are common with diffuse abdominal pain reported in 46% of patients and nausea and vomiting in up to two-thirds of patients.[42] About one-half of patients present with lethargy and stupor, but less than 25% present with loss of consciousness.[1] On physical examination, patients often present with signs of dehydration with dry mucous membranes and poor skin turgor, tachycardia, or hypotension. Patients in DKA may exhibit Kussmaul respirations and a classic fruity (acetone) breath odor (**Table 2**).

Laboratory Findings

The syndrome of DKA consists of the triad of hyperglycemia, ketonemia, and metabolic acidosis (**Table 3**). The American Diabetes Association classifies DKA by severity as mild, moderate, or severe depending on the degree of acidosis (along with decrease in bicarbonate) and altered sensorium.[1] Most patients with DKA present with mild to moderate DKA with a blood glucose greater than 250 mg/dL, bicarbonate between 10 and 18 mEq/L, arterial pH of greater than 7.3, high ketones in the urine or blood, and increased anion gap metabolic acidosis of greater than 12.

The anion gap is calculated with the following formula: sodium [Na^+] – chloride [Cl^-] + bicarbonate [HCO_3^-]. Although the majority of patients present with plasma glucose levels of greater than 250 mg/dL, some patients exhibit only mild elevations in plasma glucose levels (termed 'euglycemic DKA').[78] This phenomenon has been reported during pregnancy, in patients with prolonged starvation, alcohol intake, partially treated patients receiving insulin, and more recently in the setting of SGLT-2 inhibitor use.[57,79,80]

The key diagnostic criterion is an elevation in circulating total blood ketone and high anion gap metabolic acidosis of greater than 12. Assessment of ketonemia can be performed by the nitroprusside reaction in urine or serum, which provides a

Table 2
Clinical features of hyperglycemic emergencies

Condition	Symptoms	Signs	Presentation
DKA	Polydipsia	Hypothermia	Acute onset (hours-days)
	Polyuria	Tachycardia	More common in T1D than T2D
	Weakness	Tachypnea	
	Weight loss	Kussmaul breathing	
	Nausea	Ileus	
	Vomiting	Acetone breath	
	Abdominal pain	Altered sensorium	
HHS	Polydipsia	Hypothermia	Insidious onset (days-weeks)
	Polyuria	Hypotension	Older age
	Weakness	Tachycardia	More common in T2D than T1D
	Weight loss	Altered sensorium	

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 3
Diagnostic criteria for DKA and HHS

	DKA			
Measure	**Mild**	**Moderate**	**Severe**	**HHS**
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25 to 7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to < 15	<10	>18
Urine or serum ketones[a]	Positive	Positive	Positive	Small
Urine or serum β-hydroxybutyrate (mmol/L)	>3.0	>3.0	>3.0	<3.0
Effective serum osmolality[b]	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state.
[a] Nitroprusside reaction.
[b] Effective serum osmolality: 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18.
Adapted from Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1336; with permission.

semiquantitative estimation of acetoacetate and acetone levels. The nitroprusside test is highly sensitive, but it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of β-hydroxybutyrate, the main metabolic product in ketoacidosis.[67,81] Therefore, direct measurement of serum β-hydroxybutyrate is preferred for diagnosis.[82]

DIAGNOSIS OF HYPERGLYCEMIC HYPEROSMOLAR STATE

Symptoms and Signs

The majority of patients with HHS present with a history of polyuria, polydipsia, weakness, blurred vision, and progressive decline in mental status.[50,83] The typical patient with HHS is older than 60 years of age with an infection or acute illness who has delayed seeking medical attention. On physical examination, similar to DKA, patients with HHS frequently have clear signs of dehydration, dry mucous membranes and poor skin turgor, or hypotension.[50]

Laboratory Findings

The diagnostic criteria for HHS includes a plasma glucose of greater than 600 mg/dL, and effective osmolality of greater than 320 mOsm/kg, and the absence of ketoacidosis.[1] Effective osmolality is calculated with the following formula: sodium ion (mEq/L) × 2 + glucose (mg/dL)/18. Although by definition HHS is characterized by a pH of greater than 7.3, a bicarbonate of greater than 18 mEq/L, and negative ketone bodies, mild to moderate ketonemia may be present. Patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or to an increase in serum lactate levels or renal failure.[21]

COMMON LABORATORY PITFALLS

Patients with DKA frequently present with significant leukocytosis with white cell counts in the 10,000 to 15,000 mm^3 range. A leukocyte count of greater than 25,000 mm^3 or the presence of greater than 10% neutrophil bands is seldom seen

in the absence of bacterial infection.[64,84] In ketoacidosis, leukocytosis is attributed to stress, dehydration, and demargination of leukocytes.

The admission serum sodium may be low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose greater than 100 mg/dL.[1] An increase in serum sodium concentration in the presence of severe hyperglycemia indicates a profound degree of dehydration and water loss.

The admission serum potassium concentration is usually elevated in patients with DKA and HHS.[64] In a several studies,[1,39,85] the mean serum potassium in patients with DKA and HHS was 5.6 mEq/L and 5.7 mEq/L, respectively. These high levels occur because of a shift of potassium from the intracellular to the extracellular space owing to insulin deficiency and hypertonicity, as well as academia in DKA.[86] It is important to keep in mind that, during insulin treatment and fluid administration, potassium levels decrease owing to a shift back to the intracellular space, which may result in hypokalemia.

Similarly, serum phosphate levels in patients with DKA do not reflect the actual body deficit that uniformly exists, because phosphate shifts from the intracellular to the extracellular space owing to insulin deficiency, hypertonicity, and catabolic state. Dehydration also can lead to increases in total serum protein, albumin, amylase, and creatinine phosphokinase concentration in patients with hyperglycemic crises.

Not all patients who present with ketoacidosis have DKA. Patients with chronic ethanol abuse with a recent binge culminating in nausea, vomiting, and acute starvation may present with alcoholic ketoacidosis. The key diagnostic feature that differentiates diabetic and alcohol-induced ketoacidosis is the concentration of blood glucose.[87] The presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of alcoholic ketoacidosis. In addition, some patients with decreased food intake and caloric intake of lower than 500 calories per day for several days may present with starvation ketosis. Patients with starvation ketosis rarely present with a serum bicarbonate concentration of less than 18 mEq/L because of the slow onset of ketosis that allows increased ketone clearance by peripheral tissue (brain and muscle) and enhancement of the kidney's ability to excrete ammonia to compensate for the increased acid production.[88]

MANAGEMENT OF HYPERGLYCEMIC CRISES

The American Diabetes Association algorithm for the management of hyperglycemic emergencies is shown in **Fig. 2**.[1] Similar therapeutic measures are recommended for the treatment of DKA and HHS. In general, treatment goals include correction of dehydration, hyperglycemia, hyperosmolality, electrolyte imbalance, and increased ketonemia, and the identification and treatment of precipitating event(s). The average time to resolution is between 10 and 18 hours for DKA[89,90] and approximately 9 and 11 hours for HHS.[4] During treatment, frequent monitoring of vital signs, volume, and rate of fluid administration, insulin dosage, and urine output are needed to assess response to medical treatment. In addition, laboratory measurements of glucose and electrolytes, venous pH, bicarbonate, and anion gap should be repeated every 2 to 4 hours.[91]

Most patients with uncomplicated DKA can be treated in the emergency department or in stepdown units if close nursing supervision and monitoring is available. Several studies have failed to demonstrate clear benefits in treating DKA patients in the intensive care unit (ICU) compared with stepdown units.[92–94] The mortality rate, duration of

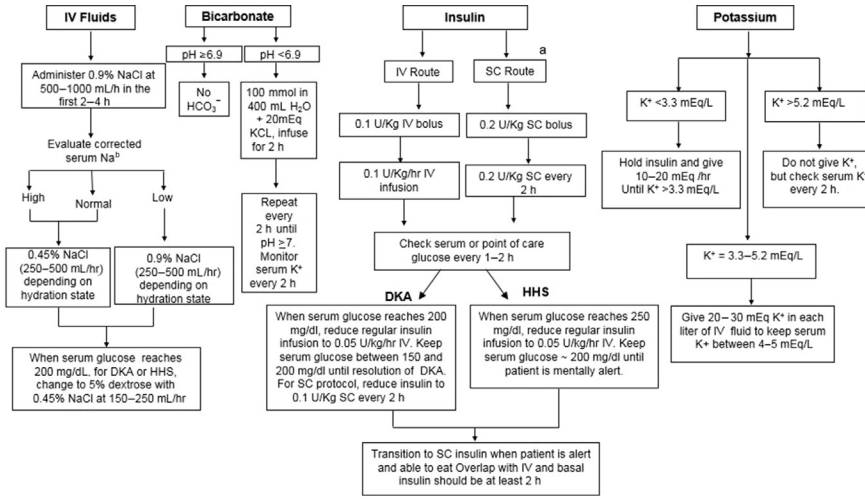

Fig. 2. Management of hyperglycemic emergencies. [a] Subcutaneous insulin protocol has not been validated for a hyperglycemic hyperosmolar state (HHS). [b] Correct serum sodium by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose above 100 mg/dL. DKA, diabetic ketoacidosis; IV, intravenous; SC, subcutaneous. (*Adapted from* Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1339; with permission.)

hospital stay, or time to resolve ketoacidosis are similar between patients treated in ICU and non-ICU settings. In addition, ICU admission has been associated with more laboratory testing and higher hospitalization cost in patients with DKA.[36,92] Patients with mild to moderate DKA can be managed safely in the emergency department or in stepdown units, and only patients with severe DKA or those with a critical illness as precipitating cause (ie, myocardial infarction, gastrointestinal bleeding, sepsis)[1,95] should be treated in the ICU. Because patients with HHS frequently present with altered mental status and have significantly higher mortality than patients with DKA, we recommend that patients with HHS be managed in the ICU.

FLUID THERAPY

Intravenous (IV) fluids are a critical aspect of treatment of hyperglycemic emergencies. Treatment with IV fluids alone expands intravascular volume, restores renal perfusion, and reduces insulin resistance by decreasing circulating counterregulatory hormone levels.[62] Isotonic saline (0.9% NaCl) is the preferred solution and is given at an initial rate of 500 to 1000 mL/h during the first 2 to 4 hours. A study comparing 2 IV fluid regimens with sodium chloride and lactate ringers found no significant difference in time to resolution of DKA, but the time to correct hyperglycemia was significantly longer in the lactated Ringers' group.[96] After intravascular volume depletion has been corrected, the rate of normal saline infusion should be reduced to 250 mL/h or changed to 0.45% saline (250–500 mL/h) depending on the serum sodium concentration and state of hydration.[1] Once the plasma glucose level reaches approximately 200 mg/dL (11.1 mosm/L), replacement fluids should contain 5% to 10% of dextrose to allow continued insulin administration until ketonemia is corrected, while avoiding hypoglycemia.[97] Adequate fluid resuscitation is of particular importance in management of HHS, because many of these patients may see improvement in or resolution of mental status changes with correction of fluid deficits.[83]

Potassium

Metabolic acidosis and insulin deficiency both lead to extracellular movement of potassium. Thus, although serum potassium levels may be normal or increased in DKA, patients are actually total body depleted. Similarly, HHS is associated with total body potassium depletion owing to lack of insulin and increased plasma osmolality.[20,86] The total body potassium deficit has been estimated to be approximately 3 to 5 mEq/kg.[85,98] Insulin therapy lowers serum potassium levels by promoting the movement of potassium back into the intracellular compartment. Thus, potassium replacement should be started when the serum concentration is less than 5.2 mEq/L to maintain a level of 4 to 5 mEq/L. The administration of 20 to 30 mEq of potassium per liter of fluids is sufficient for most patients; however, lower doses are required for patients with acute or chronic renal failure. Among patients with admission hypokalemia, with serum potassium levels of less than 3.3 mEq/L, insulin administration may result in severe symptomatic hypokalemia with muscle weakness and increased risk of cardiac arrhythmias. In such patients, potassium replacement should begin at a rate of 10 to 20 mEq/h and insulin therapy should be delayed until the potassium level increases to greater than 3.3 mEq/L.

Bicarbonate

The routine administration of bicarbonate has not been shown to improve clinical outcomes, such as time to resolution, duration of hospital stay, or mortality in patients with DKA[99–102] and is generally only recommended in patients with life-threatening acidosis with a pH of less than 6.9. Bicarbonate therapy may increase the risk of hypokalemia and cerebral edema.[103,104] Although no studies have looked at the effect of bicarbonate therapy in patients with severe acidosis, because of the potential risk of reduced cardiac contractility and arrhythmias, clinical guidelines recommend the administration of 50 to 100 mmol of sodium bicarbonate as an isotonic solution (in 400 mL of water) until pH is greater than 6.9. In patients with mild DKA with pH of greater than 7.0 or with HHS, bicarbonate therapy is not indicated.

Insulin Regimens

Insulin administration is the mainstay of DKA therapy because it lowers the serum glucose by inhibiting endogenous glucose production and increasing peripheral use. Insulin also inhibits lipolysis, ketogenesis, and glucagon secretion, thereby decreasing the production of ketoacidosis.

A continuous IV infusion of regular insulin is the treatment of choice. Most treatment protocols recommend the administration of 0.1 U/kg body weight bolus followed by continuous insulin infusion at 0.1 U/kg per hour until blood glucose is approximately 200 mg/dL (see **Fig. 2**). At this point, the dose is reduced by one-half (0.05 U/kg per hour) and rate is adjusted between 0.02 to 0.05 U/kg per hour, along with the addition of 5% dextrose, to maintain glucose concentrations between 140 and 200 mg/dL until resolution of ketoacidosis.[1]

Several studies have demonstrated that the administration of subcutaneous doses of rapid insulin analogs (Lispro and Aspart) every 1 to 2 hours is an effective alternative to the IV infusion of regular insulin in terms of time to resolution of DKA.[105–107] Patients are treated with an initial bolus of 0.2 to 0.3 U/kg followed by 0.1 to 0.2 U/kg every 1 to 2 hours, respectively until glucose is less than 250 mg/dL. The dose is then reduced by one-half to 0.05 U/kg every 1 hour or 0.01 U/kg every 2 hours until the resolution of DKA.[89,105] Using scheduled subcutaneous insulin allows for safe and effective treatment in the emergency room and stepdown units without the need for ICU care.

The use of intramuscular injections of rapid-acting insulin is also effective in the treatment of DKA, but this route tends to be more painful than subcutaneous injection and might increase the risk of bleeding among patients receiving anticoagulation therapy.[97,108] It is important to keep in mind that the use of rapid-acting subcutaneous insulin analogues is not recommended for patients with arterial hypotension, severe and complicated DKA, or with HHS.

TRANSITION TO MAINTENANCE INSULIN REGIMEN

Resolution of DKA is defined when glucose levels are lower than 250 mg/dL, venous pH is greater than 7.30, there is a normal anion gap, and serum bicarbonate is 18 mEq/L or greater.[1] HHS resolution is achieved when effective serum osmolality is less than 310 mOsm/kg and the glucose level is 250 mg/dL or less (13.8 mmol/L) in a patient who has recovered mental alertness and regaining of mental status.[1,97]

Because of the short half-life of intravenous insulin (<10 minutes),[109] abrupt cessation of the insulin may result is rebound hyperglycemia, ketogenesis, and recurrent metabolic acidosis. Subcutaneous basal insulin (NPH, Glargine, Detemir, Degludec), should be given at least 2 hours before discontinuing the IV insulin infusion.[1] Earlier initiation, 3 to 4 hours before discontinuation of insulin drip, should be considered when using basal insulin analogues (Glargine, Determir, Degludec), which have a longer delay in onset of action than NPH insulin. One randomized controlled trial evaluated the effect of coadministration of IV insulin with subcutaneous Glargine shortly after the onset of treatment of DKA compared with IV insulin alone.[110] Patients who received Glargine had a trend towards shorter time to resolution of DKA (based on closure of anion gap) and shorter duration of hospital stay; however, these differences were not statistically significant.[110] Another study found that the administration of Glargine early in the course of treatment reduced the frequency of rebound hyperglycemia after transition off of insulin drip.[111]

For insulin-naïve patients, a starting total daily insulin dose of 0.5 to 0.6 U/kg may be started (one-half as basal and one-half as bolus).[1] Patients with poor oral intake should receive basal insulin alone or, alternatively, may be continued on an insulin drip until they are able to eat. Patients with known diabetes can be restarted on their previous insulin regimens; however, an adjustment of the previous regimen should be considered if there is a history of frequent hypoglycemia, or significantly uncontrolled hyperglycemia before admission, as indicated by admission HbA1c. Multidose insulin regimens with basal insulin and prandial rapid-acting insulin analogues are the preferred insulin regimen for patients with T1D and DKA, and for most patients with HHS. A randomized, controlled trial in DKA patients compared transition regimens of NPH and regular insulin twice daily versus Glargine once daily and Glulisine before meals found similar glycemic control between the 2 groups; however, the NPH/regular insulin group had more than double the rate of hypoglycemia (<70 mg/dL) compared with the Glargine/Glulisine group.[112]

COMPLICATIONS

Hypoglycemia is the most common complication during treatment, reported in 5% to 25% of patients with DKA.[1,4,105] Lack of frequent monitoring and the failure to reduce insulin infusion rate and/or to use dextrose-containing solutions when blood glucose levels are less than 200 mg/dL are the most important risk factors associated with hypoglycemia during insulin treatment. Many patients with hypoglycemia do not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger, and tachycardia, and thus frequent blood glucose monitoring (every 1 to 2 hours) is

mandatory.[97] Acute adverse outcomes of hypoglycemia include seizures, arrhythmias, and cardiovascular events. Clinicians should be aware that recurrent episodes of hypoglycemia might be associated with a state of hypoglycemia unawareness (loss of perception of warning symptoms of developing hypoglycemia), which may complicate diabetes management after the resolution of hyperglycemic crises.

Hypokalemia is the second most common complication during DKA and HHS treatment.[4] Although the admission serum potassium concentration is commonly elevated, during insulin treatment, the plasma concentration of potassium will invariably decrease owing to increased cellular potassium uptake in peripheral tissues.[1] Thus, to prevent hypokalemia, replacement with IV potassium when concentration is less than 5.2 mEq/L is indicated. In patients admitted with reduced serum potassium less than 3.3 mEq/L, IV potassium replacement should begin immediately and insulin therapy should be held until serum potassium is 3.3 mEq/L or greater to avoid severe hypokalemia.

Cerebral edema is rare in adults, but is reported in approximately 1% of children with DKA with a mortality rate between 20% and 40%.[103,113] The pathogenesis of cerebral edema is incompletely understood. Evidence for disruption of the blood–brain barrier has been found in cases of fatal cerebral edema.[103,114] The degree of edema formation during DKA in children correlates with the degree of dehydration and hyperventilation at presentation, but it does not correlate with initial osmolality, osmotic changes during treatment, or rate of fluid or sodium administration.[115] Clinically significant cerebral edema usually develops 4 to 12 hours after treatment has started, but it can occur as late as 24 to 48 hours after the start of treatment. Clinical criteria include altered mentation or fluctuating level of consciousness, abnormal motor or verbal response to pain, decorticate or decerebrate posturing, cranial nerve palsy (especially III, IV, and VI), and an abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne–Stokes respiration). Recommended treatment includes the administration of mannitol 0.5 to 1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes.[116,117] Hypertonic saline (3%), 5 to 10 mL/kg over 30 minutes, may be an alternative to mannitol, especially if there is no initial response to mannitol.[118] After treatment for cerebral edema has been started, a cranial computed tomography scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (approximately 10% of cases), especially thrombosis and cerebral infarction, hemorrhage, or dural sinus thrombosis, which may benefit from specific therapy.[113,119–121] Corticosteroid and diuretic therapy are of no proven benefits in the treatment of cerebral edema in DKA patients.[122]

Rhabdomyolysis may occur in patients with DKA and more commonly with HHS resulting in increased risk of acute kidney failure. The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine, and monitoring creatine kinase concentrations every 2 to 3 hours is recommended for early detection.

PREVENTION

Medication noncompliance is a leading cause of DKA among both newly diagnosed and recurrent episodes of DKA.[39–41] The mean cost of hospitalization is about $7500.[40] In one-half of such episodes, patients report an inability to afford medication or to pay for transportation as the reason why medication was discontinued.[41] Development of system-wide changes such as assistance programs to provide insulin to patients and reduce lapses in treatment may be a cost-effective way to reduce the rate of hospitalization for hyperglycemic emergencies.

Multidisciplinary approaches with the use of clinical diabetes educators in close contact with and easily accessible to the patients has been shown to reduce the number of hospitalizations related to hyperglycemic emergencies.[123] Systems-based methods to reduce preventable causes of hyperglycemic emergencies may represent an important next step in reducing costs and improving patient care.

REFERENCES

1. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32(7):1335–43.
2. Centers for Disease Control and Prevention. Mortality due to Hyperglycemic crises. 2013. Available at: http://www.cdc.gov/diabetes/statistics/complications_national.htm. Accessed September 2, 2016.
3. Ennis ED, Stahl EJVB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. Diabetes Rev 1994;2:115–26.
4. Umpierrez GE, Kelly JP, Navarrete JE, et al. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157(6):669–75.
5. von Stosch A. Versuch einer Pathologie und Therapie des Diabetes Mellitus. Berlin: Duncker und Humblot; 1828 [in German].
6. Parsons J. Case of infantile diabetes. Prov Med Surg J 1849;13(13):342–3.
7. Hindle R. Case of acute diabetes. Prov Med Surg J 1845;9(29):452–3.
8. Favell CF. Cases of diabetes. Prov Med J Retrosp Med Sci 1843;6(153):467–9.
9. Kussmaul A. Zur lehre vom diabetes mellitus. Dtsch Arch Klin Med 1874;14:1–46 [in German].
10. Adolf Kussmaul (1822-1902)–Country Doctor to Clinical Professor. JAMA 1964;189:58–9.
11. Stadelmann E. Ueber die Ursachen der pathologischen ammoniakausscheidung beim diabetes mellitus und des coma diabeticum. Arch Exp Pathol Pharmakol 1883;17:419–44 [in German].
12. Külz E. Ueber eine neue linksdrehende saure (pseudo-oxybuttersaure). Zeitschr f Biologie 1884;20:165–78 [in German].
13. Dreschfeld J. The Bradshawe lecture on diabetic coma. Br Med J 1886;2(1338):358–63.
14. Banting FG, Best CH, Collip JB, et al. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. Can Med Assoc J 1962;87(20):1062–7.
15. Rabinowitch IM. Diabetic coma and diabetic mortality rates. Can Med Assoc J 1929;21(5):583–6.
16. Clements RS Jr, Vourganti B. Fatal diabetic ketoacidosis: major causes and approaches to their prevention. Diabetes Care 1978;1(5):314–25.
17. Felig P. Diabetic ketoacidosis. N Engl J Med 1974;290(24):1360–3.
18. Graves EJ, Gillium BS. Detailed diagnosis and procedures: National Discharge Survey, 1995. National Center for Health Statistics. Vital Health Stat 13 1997;13(130):1–146.
19. Wagner A, Risse A, Brill HL, et al. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. Diabetes Care 1999;22(5):674–7.
20. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care 2014;37(11):3124–31.

21. Fadini GP, de Kreutzenberg SV, Rigato M, et al. Characteristics and outcomes of the hyperglycemic hyperosmolar non-ketotic syndrome in a cohort of 51 consecutive cases at a single center. Diabetes Res Clin Pract 2011;94(2):172–9.
22. Wang ZH, Kihl-Selstam E, Eriksson JW. Ketoacidosis occurs in both type 1 and type 2 diabetes–a population-based study from Northern Sweden. Diabet Med 2008;25(7):867–70.
23. Karges B, Rosenbauer J, Holterhus PM, et al. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. Eur J Endocrinol 2015;173(3):341–50.
24. Maahs DM, Hermann JM, Holman N, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care 2015;38(10):1876–82.
25. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38(6):971–8.
26. Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. J Pediatr 2010;156(2):180–4.
27. Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabet Med 2011;28(5):508–15.
28. Otieno CF, Kayima JK, Omonge EO, et al. Diabetic ketoacidosis: risk factors, mechanisms and management strategies in sub-Saharan Africa: a review. East Afr Med J 2005;82(12 Suppl):S197–203.
29. Bhowmick SK, Levens KL, Rettig KR. Hyperosmolar hyperglycemic crisis: an acute life-threatening event in children and adolescents with type 2 diabetes mellitus. Endocr Pract 2005;11(1):23–9.
30. Wachtel TJ, Silliman RA, Lamberton P. Prognostic factors in the diabetic hyperosmolar state. J Am Geriatr Soc 1987;35(8):737–41.
31. Basu A, Close CF, Jenkins D, et al. Persisting mortality in diabetic ketoacidosis. Diabet Med 1993;10(3):282–4.
32. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc 1992;40(11):1100–4.
33. Gibb FW, Teoh WL, Graham J, et al. Risk of death following admission to a UK hospital with diabetic ketoacidosis. Diabetologia 2016;59(10):2082–7.
34. Huang CC, Weng SF, Tsai KT, et al. Long-term mortality risk after hyperglycemic crisis episodes in geriatric patients with diabetes: a national population-based cohort study. Diabetes Care 2015;38(5):746–51.
35. Gregg EW, Williams DE, Geiss L. Changes in diabetes-related complications in the United States. N Engl J Med 2014;371(3):286–7.
36. Javor KA, Kotsanos JG, McDonald RC, et al. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. Diabetes Care 1997;20(3):349–54.
37. Klingensmith GJ, Tamborlane WV, Wood J, et al. Diabetic ketoacidosis at diabetes onset: still an all too common threat in youth. J Pediatr 2013;162(2):330–4.e1.
38. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014;133(4):e938–45.

39. Randall L, Begovic J, Hudson M, et al. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes Care 2011;34(9):1891–6.
40. Maldonado MR, Chong ER, Oehl MA, et al. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. Diabetes Care 2003;26(4):1265–9.
41. Musey VC, Lee JK, Crawford R, et al. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes Care 1995;18(4):483–9.
42. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. J Crit Care 2002;17(1):63–7.
43. Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with type 1 diabetes: systematic literature review. Diabet Med 2006;23(4):445–8.
44. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Goguen J, Gilbert J. Hyperglycemic emergencies in adults. Can J Diabetes 2013;37(Suppl 1):S72–6.
45. Garg SK, Walker AJ, Hoff HK, et al. Glycemic parameters with multiple daily injections using insulin glargine versus insulin pump. Diabetes Technol Ther 2004;6(1):9–15.
46. Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 1995;18(3):361–76.
47. Ly TT, Nicholas JA, Retterath A, et al. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310(12):1240–7.
48. Johnson SR, Cooper MN, Jones TW, et al. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 2013;56(11):2392–400.
49. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, et al. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. J Gen Intern Med 1991;6(6):495–502.
50. Gerich JE, Martin MM, Recant L. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes. 1971;20(4):228–38.
51. Ben Salem C, Fathallah N, Hmouda H, et al. Drug-induced hypoglycaemia: an update. Drug Saf 2011;34(1):21–45.
52. Caro JJ, Ward A, Levinton C, et al. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. J Clin Psychiatry 2002;63(12):1135–9.
53. Buse JB, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiol 2003;56(2):164–70.
54. Gianfrancesco F, Grogg A, Mahmoud R, et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. Clin Ther 2003;25(4):1150–71.
55. Ananth J, Parameswaran S, Gunatilake S. Side effects of atypical antipsychotic drugs. Curr Pharm Des 2004;10(18):2219–29.
56. Lipscombe LL, Austin PC, Alessi-Severini S, et al. Atypical antipsychotics and hyperglycemic emergencies: multicentre, retrospective cohort study of administrative data. Schizophr Res 2014;154(1–3):54–60.

57. Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38(9):1687–93.
58. Perspective Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100(8):2849–52.
59. Erondu N, Desai M, Ways K, et al. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care 2015;38(9): 1680–6.
60. Tang H, Li D, Wang T, et al. Effect of sodium-glucose cotransporter 2 inhibitors on diabetic ketoacidosis among patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes care 2016;39(8):e123–4.
61. Kibbey RG. SGLT-2 inhibition and glucagon: cause for alarm? Trends Endocrinol Metab 2015;26(7):337–8.
62. Waldhausl W, Kleinberger G, Korn A, et al. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. Diabetes. 1979;28(6):577–84.
63. Chupin M, Charbonnel B, Chupin F. C-peptide blood levels in keto-acidosis and in hyperosmolar non-ketotic diabetic coma. Acta Diabetol Lat 1981;18(2):123–8.
64. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001;24(1):131–53.
65. Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003;88(11):5090–8.
66. Miles JM, Rizza RA, Haymond MW, et al. Effects of acute insulin deficiency on glucose and ketone body turnover in man: evidence for the primacy of overproduction of glucose and ketone bodies in the genesis of diabetic ketoacidosis. Diabetes 1980;29(11):926–30.
67. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983;309(3):159–69.
68. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999;15(6):412–26.
69. Miles JM, Haymond MW, Nissen SL, et al. Effects of free fatty acid availability, glucagon excess, and insulin deficiency on ketone body production in postabsorptive man. J Clin Invest 1983;71(6):1554–61.
70. McGarry JD, Foster DW. Effects of exogenous fatty acid concentration on glucagon-induced changes in hepatic fatty acid metabolism. Diabetes. 1980; 29(3):236–40.
71. McGarry JD, Foster DW. Regulation of hepatic fatty acid oxidation and ketone body production. Annu Rev Biochem 1980;49:395–420.
72. Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. Free Radic Biol Med 2011;50(5):567–75.
73. Li J, Huang M, Shen X. The association of oxidative stress and pro-inflammatory cytokines in diabetic patients with hyperglycemic crisis. J Diabetes Complications 2014;28(5):662–6.
74. Vaarala O, Yki-Jarvinen H. Diabetes: should we treat infection or inflammation to prevent T2DM? Nat Rev Endocrinol 2012;8(6):323–5.
75. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27(3):813–23.

76. Kim F, Tysseling KA, Rice J, et al. Free fatty acid impairment of nitric oxide production in endothelial cells is mediated by IKKbeta. Arterioscler Thromb Vasc Biol 2005;25(5):989–94.
77. Chaudhuri A, Umpierrez GE. Oxidative stress and inflammation in hyperglycemic crises and resolution with insulin: implications for the acute and chronic complications of hyperglycemia. J Diabetes Complications 2012;26(4):257–8.
78. Jenkins D, Close CF, Krentz AJ, et al. Euglycaemic diabetic ketoacidosis: does it exist? Acta Diabetol 1993;30(4):251–3.
79. Bas VN, Uytun S, Torun YA. Diabetic euglycemic ketoacidosis in newly diagnosed type 1 diabetes mellitus during Ramadan fasting. J Pediatr Endocrinol Metab 2015;28(3–4):333–5.
80. Guo RX, Yang LZ, Li LX, et al. Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: case-control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. J Obstet Gynaecol Res 2008;34(3):324–30.
81. Stephens JM, Sulway MJ, Watkins PJ. Relationship of blood acetoacetate and 3-hydroxybutyrate in diabetes. Diabetes. 1971;20(7):485–9.
82. Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care 2008;31(4):643–7.
83. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine (Baltimore) 1972;51(2):73–94.
84. Slovis CM, Mork VG, Slovis RJ, et al. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Am J Emerg Med 1987;5(1):1–5.
85. Beigelman PM. Potassium in severe diabetic ketoacidosis. Am J Med 1973;54(4):419–20.
86. Adrogue HJ, Lederer ED, Suki WN, et al. Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine (Baltimore). 1986;65(3):163–72.
87. Umpierrez GE, DiGirolamo M, Tuvlin JA, et al. Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. J Crit Care 2000;15(2):52–9.
88. Cahill GF Jr. Starvation in man. N Engl J Med 1970;282(12):668–75.
89. Umpierrez GE, Cuervo R, Karabell A, et al. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care 2004;27(8):1873–8.
90. Hara JS, Rahbar AJ, Jeffres MN, et al. Impact of a hyperglycemic crises protocol. Endocr Pract 2013;19(6):953–62.
91. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in diabetes. Diabetes Care 2004;27(Suppl 1):S94–102.
92. May ME, Young C, King J. Resource utilization in treatment of diabetic ketoacidosis in adults. Am J Med Sci 1993;306(5):287–94.
93. Moss JM. Diabetic ketoacidosis: effective low-cost treatment in a community hospital. South Med J 1987;80(7):875–81.
94. Umpierrez GE, Latif KA, Cuervo R, et al. Subcutaneous aspart insulin: a safe and cost effective treatment of diabetic ketoacidosis. Diabetes. 2003;52(Suppl 1):584A.
95. Glaser NS, Ghetti S, Casper TC, et al, Pediatric Emergency Care Applied Research Network DKAFSG. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. Pediatr Diabetes 2013;14(6):435–46.

96. Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis–Ringer's lactate versus normal saline: a randomized controlled trial. QJM 2012;105(4):337–43.
97. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016; 12(4):222–32.
98. Abramson E, Arky R. Diabetic acidosis with initial hypokalemia. Therapeutic implications. JAMA 1966;196(5):401–3.
99. Lever E, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med 1983;75(2):263–8.
100. Green SM, Rothrock SG, Ho JD, et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. Ann Emerg Med 1998;31(1):41–8.
101. Latif KA, Freire AX, Kitabchi AE, et al. The use of alkali therapy in severe diabetic ketoacidosis. Diabetes Care 2002;25(11):2113–4.
102. Gamba G, Oseguera J, Castrejon M, et al. Bicarbonate therapy in severe diabetic ketoacidosis. A double blind, randomized, placebo controlled trial. Rev Invest Clin 1991;43(3):234–8.
103. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344(4):264–9.
104. Fraley DS, Adler S. Correction of hyperkalemia by bicarbonate despite constant blood pH. Kidney Int 1977;12(5):354–60.
105. Umpierrez GE, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004;117(5):291–6.
106. Ersoz HO, Ukinc K, Kose M, et al. Subcutaneous lispro and intravenous regular insulin treatments are equally effective and safe for the treatment of mild and moderate diabetic ketoacidosis in adult patients. Int J Clin Pract 2006;60(4): 429–33.
107. Karoli R, Fatima J, Salman T, et al. Managing diabetic ketoacidosis in non-intensive care unit setting: role of insulin analogs. Indian J Pharmacol 2011; 43(4):398–401.
108. Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Ann Intern Med 1976;84(6):633–8.
109. Hipszer B, Joseph J, Kam M. Pharmacokinetics of intravenous insulin delivery in humans with type 1 diabetes. Diabetes Technol Ther 2005;7(1):83–93.
110. Doshi P, Potter AJ, De Los Santos D, et al. Prospective randomized trial of insulin glargine in acute management of diabetic ketoacidosis in the emergency department: a pilot study. Acad Emerg Med 2015;22(6):657–62.
111. Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. J Clin Endocrinol Metab 2012;97(9):3132–7.
112. Umpierrez GE, Jones S, Smiley D, et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care 2009;32(7):1164–9.
113. Wolfsdorf J, Glaser N, Sperling MA, American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29(5):1150–9.

114. Hoffman WH, Stamatovic SM, Andjelkovic AV. Inflammatory mediators and blood brain barrier disruption in fatal brain edema of diabetic ketoacidosis. Brain Res 2009;1254:138–48.
115. Glaser NS, Wootton-Gorges SL, Buonocore MH, et al. Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols. Pediatrics 2013;131(1):e73–80.
116. Shabbir N, Oberfield SE, Corrales R, et al. Recovery from symptomatic brain swelling in diabetic ketoacidosis. Clin Pediatr (Phila) 1992;31(9):570–3.
117. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes 2001;2(3):109–14.
118. Kamat P, Vats A, Gross M, et al. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. Pediatr Crit Care Med 2003;4(2):239–42.
119. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr 2002; 141(6):793–7.
120. Roe TF, Crawford TO, Huff KR, et al. Brain infarction in children with diabetic ketoacidosis. J Diabetes Complications 1996;10(2):100–8.
121. Keane S, Gallagher A, Ackroyd S, et al. Cerebral venous thrombosis during diabetic ketoacidosis. Arch Dis Child 2002;86(3):204–5.
122. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13(1):22–33.
123. Deeb A, Yousef H, Abdelrahman L, et al. Implementation of a diabetes educator care model to reduce paediatric admission for diabetic ketoacidosis. J Diabetes Res 2016;2016:3917806.