

# 14 Emergencies in Diabetes Mellitus

**Abstract:** Identification and management of emergencies in diabetes is important to prevent mortality. Three major life-threatening complications encountered are (i) diabetic ketoacidosis (ii) hyperosmolar hyperglycemic state and (iii) hypoglycemia. Diabetic ketoacidosis is a triad of uncontrolled hyperglycemia, metabolic acidosis and increased ketones concentration. Ketoacidosis usually results from insulin deficiency and excess counter regulatory hormones. Severe hyperglycemia ensues as a result of increased neoglucogenesis, accelerated glycogenolysis and impaired glucose use by peripheral tissues. Management of diabetic ketoacidosis consists of fluid replacement, correction of hyperglycemia and metabolic acidosis, electrolyte replacement, detection and proper treatment of precipitating causes. Hyperosmolar hyperglycemic state is characterized by gradual development of marked hyperglycemia, dehydration and prerenal uremia without significant ketosis and acidosis. Treatment includes aggressive rehydration and electrolyte replacement. On the other hand hypoglycemia is associated with sudden death caused by arrhythmia (the dead-in-bed syndrome). Hypoglycemia if remains more than few minutes may lead to central nervous system dysfunction, impaired cognition and eventually coma. It should be treated immediately with oral glucose or if patient is unconscious by intravenous glucose or glucagon injection.

## **HYPERGLYCEMIC CRISIS— DIABETIC KETOACIDOSIS**

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two of the most serious acute metabolic complications of diabetes. Most patients with DKA have type 1 diabetes; however, patients with type 2 diabetes are also at risk during the stress of acute illness such as trauma, surgery, or infection. The triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration characterizes DKA. These metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Successful treatment of DKA requires frequent monitoring of patients, improvement of circulatory volume and tissue perfusion, correction of hypovolemia and hyperglycemia, replacement of electrolyte losses, and a careful search for the precipitating cause.<sup>1</sup>

### **Epidemiology**

Diabetic ketoacidosis is present in approximately 25 of 40% of diabetic children and adolescents and in 15 to 20% of adult patients at the time of diagnosis of diabetes.<sup>2,3</sup> The mortality rate in patients with DKA is <5% in experienced centers, whereas the mortality rate of patients with HHS still remains high at about 11%. Death in these conditions is rarely due to the metabolic

complications of hyperglycemia or ketoacidosis but rather relates to the underlying precipitating illness. The prognosis of both conditions is substantially worsened at the extremes of age and in the presence of coma and hypotension.

### **Precipitating Causes**

In known diabetic patients, precipitating factors for DKA include infections, intercurrent illnesses, psychological stress, and noncompliance with therapy (Table 1). Worldwide, infection remains the most common underlying cause, occurring in 30 to 50% of cases and urinary tract infection and pneumonia account for the majority of infections.<sup>3</sup> Drugs that affect carbohydrate metabolism can also be responsible. Poor compliance with therapy is a major precipitating cause for DKA in indigent patients.<sup>3</sup> In a recent report, the most common cause of DKA was stopping insulin therapy, which occurred in 67% of episodes.<sup>4</sup>

### **Pathogenesis**

DKA is a state of severe metabolic decompensation characterized by hyperglycemia, metabolic acidosis, and increased total ketone bodies or ketoacids. Ketoacidosis results from insulin deficiency and excess counter regulatory hormones including glucagon, catecholamines, cortisol, and growth hormone.<sup>5, 6</sup> The insulin deficiency of DKA can be absolute, as is usually the case in patients with autoimmune type 1 diabetes, or the insulin deficiency can be relative, as in patients with type 2 diabetes. Various pathogenic mechanisms include:

- When insulin is deficient, hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues.<sup>7,8</sup>
- Increased hepatic glucose production results from the high availability of gluconeogenic precursors, such as amino acids, lactate, and glycerol, and increased activity of gluconeogenic enzymes (phosphoenol pyruvate carboxykinase (PEPCK), fructose 1, 6-bisphosphatase, and pyruvate carboxylase).<sup>8</sup>
- Amino acids (alanine and glutamine) increase as a result of accelerated proteolysis and decreased protein synthesis.
- Lactate increases as a result of increased muscle glycogenolysis, and glycerol increases as a result of increased lipolysis.
- Elevated glucagon and catecholamine levels lead to increased gluconeogenesis and glycogenolysis. High cortisol levels stimulate protein catabolism and increased concentration of circulating amino acids, providing precursors for gluconeogenesis. In addition to increased glucose production, the combination of low insulin concentration and high levels of counter regulatory hormones impairs glucose uptake in peripheral tissues.
- Hyperglycemia causes an osmotic diuresis that contributes to hypovolemia and decreases glomerular filtration rate, and this in turn increases the severity of the hyperglycemia.
- The increased activity of tissue lipase causes breakdown of triglyceride into glycerol and free fatty acids. Once released, glycerol serves as a carbon skeleton for gluconeogenesis in the liver, but it is the increased release of free fatty acids that constitutes the primary mechanism for ketoacid production. In the liver, free fatty acids are oxidized to ketone bodies, a process predominantly stimulated by glucagon.
- Increased concentration of glucagon in DKA lowers the hepatic levels of malonyl coenzyme A (CoA), the first rate-limiting enzyme in *de novo* fatty acid synthesis. Malonyl CoA inhibits carnitine palmitoyl transferase 1 (CPT-1), the rate-limiting enzyme for transesterification of fatty acyl CoA to fatty acyl carnitine, a step that subsequently allows oxidation of fatty acids to ketone bodies at the level of the mitochondria. The increased fatty acyl CoA and CPT-1

activity in DKA leads to increased ketogenesis in DKA. In addition to increased production of ketone bodies, there is evidence that clearance of ketones is decreased in patients with DKA.<sup>9</sup>

- *Inflammatory response:* Hyperglycemia in patients with DKA is also associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines, reactive oxygen species (ROS), and cardiovascular risk factors in the absence of obvious infection or cardiovascular pathology.<sup>1</sup>

## DIAGNOSIS

### History and Physical Examination

The evolution of the acute DKA episode in type 1 diabetes or even in type 2 diabetes tends to be short. Although the symptoms of poorly controlled diabetes may be present for several days, the metabolic alterations typical of ketoacidosis usually evolve within a short time frame (typically <24 h). The classic clinical picture of patients with DKA includes a history of polyuria, polydipsia, weight loss, vomiting, abdominal pain, dehydration, weakness, mental status change, and coma (Table 2).

Physical findings may include poor skin turgor, Kussmaul respirations, tachycardia, hypotension, alteration in mental status, shock, and ultimately coma. Up to 25% of DKA patients have emesis, which may be coffee-ground in appearance. Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS. Although infection is a common precipitating factor for both DKA and HHS, patients can be normothermic or even hypothermic primarily because of peripheral vasodilation; severe hypothermia, if present, is a poor prognostic sign. Abdominal pain, sometimes mimicking an acute abdomen, is present in 50-75% of DKA cases. The abdominal pain usually resolves with correction of hyperglycemia and metabolic acidosis.<sup>10</sup>

### Laboratory Findings

DKA consists of the biochemical triad of hyper-glycemia, ketonemia, and metabolic acidosis. The most widely used diagnostic criteria for DKA have been blood glucose greater than 250 mg/dL, serum bicarbonate lower than 15 mEq/L, arterial pH lower than 7.3, an increased anion gap metabolic acidosis, and a moderate degree of ketonemia. Although these criteria served well for research purposes, they have significant limitations in clinical practice because the majority of patients with DKA present with mild metabolic acidosis despite elevated serum glucose and  $\beta$ -hydroxybutyrate concentrations. The biochemical criteria for diagnosis have been modified in the American Diabetes Association (ADA) guidelines for management of hyperglycemic crises. The severity of DKA is now classified as mild, moderate, or severe; based primarily on the severity of metabolic acidosis (blood pH, bicarbonate, ketones) and the presence of altered mental status (Table 3). Standards of care call for the use of arterial pH to assess the degree of acidosis; however, venous pH is a good alternative in clinical practice because it obviates a painful procedure and decreases the risk of vascular compromise. The venous pH typically is 0.05 points less than the arterial pH. The severity of metabolic acidosis bears small relation to the degree of hyperglycemia, and cases of relative normoglycemic ketoacidosis (<250 mg/dL) have been reported.<sup>1,3</sup>

The key diagnostic feature is the elevation in circulating total blood ketone concentration. Assessment of augmented ketonemia is usually performed by the nitroprusside reaction (Ketostix), which provides a semiquantitative estimation of acetoacetate and acetone levels. Although the nitroprusside test (both in urine and in serum) is highly sensitive, it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of  $\beta$ -hydroxybutyrate, the main metabolic product in ketoacidosis. Direct measurement of  $\beta$ -

hydroxybutyrate is now available by finger-stick method and may be a more accurate indicator of severity of ketoacidosis.<sup>8</sup>

The majority of patients with hyperglycemic emergencies present with leukocytosis proportional to blood ketone body concentration. However, leukocytosis >25,000 may designate infection and require further evaluation.<sup>3</sup> The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increase in serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of water loss. Unless the plasma is cleared of chylomicrons, pseudonormoglycemia and pseudohyponatremia may occur in DKA. Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia. Patients with low normal or low serum potassium concentration on admission have severe total body potassium deficiency and require very careful cardiac monitoring and more vigorous potassium replacement, because treatment lowers potassium further and can provoke cardiac dysrhythmia. Accumulation of ketoacids results in an increased anion gap metabolic acidosis.

The plasma anion gap is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium), using the following formula: Anion gap =  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ . The normal anion gap has been historically reported to be  $12 \pm 2$  mEq/L. An anion gap greater than 10 to 12 mEq/L indicates increased anion gap acidosis.<sup>11</sup>

Studies on serum osmolality and mental alteration have established a positive linear relationship between osmolality and mental obtundation. The occurrence of stupor or coma in diabetic patients in the absence of definitive elevation of effective osmolality (320 mOsm/kg) demands immediate consideration of other causes of mental status change. In the calculation of effective osmolality the measured Na(mEq/lit) and glucose conc in (mg/dL) is taken into consideration,<sup>18</sup> is not taken into account because it is freely permeable and its accumulation does not induce major changes in intracellular volume or osmotic gradient across the cell membrane. Amylase levels are elevated in the majority of patients with DKA, but this may be due to nonpancreatic sources, such as the parotid gland. A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis; however, lipase could also be elevated in DKA. Finally, abnormal acetoacetate levels may falsely elevate serum creatinine if the clinical laboratory uses a colorimetric method for the creatinine assay.<sup>3</sup>

## Differential Diagnosis

Not all patients with ketoacidosis have DKA. Starvation ketosis and alcoholic ketoacidosis are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely > 200 mg/dl) to hypoglycemia. In addition, although alcoholic ketoacidosis can result in profound acidosis, the serum bicarbonate concentration in starvation ketosis is usually not <18 mEq/l. DKA must also be distinguished from other causes of high anion gap metabolic acidosis, including lactic acidosis; ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde; and chronic renal failure.

## TREATMENT

Successful treatment of DKA requires correction of dehydration, hyperglycemia, and electrolyte imbalances; identification of comorbid precipitating events; and above all, frequent patient monitoring.

### Fluid Therapy

Initial fluid therapy is directed towards expansion of the intravascular and extravascular volume and restoration of renal perfusion. In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15-20 ml/kg body weight/hour or 1-1.5 liters during the first hour.

The subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% NaCl infused at 4-14 ml/kg body wt/hour is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low. Successful progress with fluid replacement is judged by hemodynamic monitoring (improvement in blood pressure), measurement of fluid input and output, laboratory values, and clinical examination. Fluid replacement should correct estimated deficits within the first 24 hours. In patients with renal or cardiac compromise, monitoring of serum osmolality and frequent assessment of cardiac, renal, and mental status must be performed during fluid resuscitation to avoid iatrogenic fluid overload. Adequate rehydration with subsequent correction of the hyperosmolar state has been shown to result in a more robust response to low-dose insulin therapy.

### **Insulin Therapy**

Unless the episode of DKA is uncomplicated and mild/moderate (Table 3), regular insulin by continuous intravenous infusion is the treatment of choice. In adult patients, once hypokalemia ( $K^+ < 3.3$  mEq/l) is excluded, an intravenous bolus of regular insulin at 0.1 unit/kg body wt, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/hr should be administered. This low dose of insulin usually decreases plasma glucose concentration at a rate of 50-75 mg/dl/hr, similar to a higher dose insulin regimen. If plasma glucose does not decrease by 50-75 mg from the initial value in the first hour, the insulin infusion may be doubled every hour until a steady glucose decline is achieved. When the plasma glucose reaches 200 mg/dl in DKA it may be possible to decrease the insulin infusion rate to 0.05-0.1 unit/kg/hr at which time dextrose may be added to the intravenous fluids.<sup>1</sup> Thereafter, the rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain the above-glucose values until acidosis in DKA or mental obtundation and hyperosmolality in HHS are resolved.

### **Role of Insulin Analogues**

There were no differences in length of hospital stay, total amount of insulin administration until resolution of hyperglycemia or ketoacidosis, or number of hypoglycemic events with the use of rapid acting insulin analogues. In addition, the use of insulin analogues may allow treatment of DKA in general wards or in the emergency department, avoiding admission to an intensive care unit thereby decreasing the 30% cost of hospitalization.

### **Insulin at Resolution**

Criteria for resolution of DKA include glucose  $< 200$  mg/dl, serum bicarbonate  $> 18$  mEq/l, and venous pH  $> 7.3$ . When the patient is able to eat, a multiple dose insulin schedule should be started that uses a combination of short or rapid acting and intermediate or long-acting insulin as needed to control plasma glucose. Intravenous insulin infusion should be continued for 1-2 hours after the subcutaneous insulin is given to ensure adequate plasma insulin levels. An abrupt discontinuation of intravenous insulin coupled with a delayed onset of a subcutaneous insulin regimen may lead to hyperglycemia or recurrence of ketoacidosis. If the patient is to remain fasting, it is preferable to continue the intravenous insulin infusion and fluid replacement. Patients with known diabetes may be given insulin at the dose they were receiving before the onset of DKA. In insulin-naive patients, a multi dose insulin regimen should be started at a dose of 0.5-0.8 units/kg/day, including regular or rapid-acting and basal insulin until an optimal dose is established. However, good clinical judgment and frequent glucose assessment are vital in initiating a new insulin regimen in insulin-naive patients.

### **Potassium**

Despite total-body potassium depletion, mild-to-moderate hyperkalemia is not uncommon in patients with hyperglycemic crises. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentration. To prevent hypokalemia, potassium replacement is initiated after serum levels decrease to  $<5.3$  mEq/l, assuming the presence of adequate urine output (50 ml/h). Generally, 20-30 mEq potassium in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range of 4-5 mEq/l. Rarely, DKA patients may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to  $>3.3$  mEq/l to avoid arrhythmias or cardiac arrest and respiratory muscle weakness.

### **Bicarbonate**

Bicarbonate use in DKA remains controversial. At a pH  $> 7.0$ , administration of insulin blocks lipolysis and resolves ketoacidosis without any added bicarbonate. However, the administration of bicarbonate may be associated with several deleterious effects including an increased risks of hypokalemia, decreased tissue oxygen uptake, and cerebral edema. If the pH is 6.9-7.0, it seems prudent to administer 50 mmol bicarbonate in 200 ml of sterile water with 10 mEq KCl over 1 h until the pH is  $>7.0$ . No prospective randomized studies concerning the use of bicarbonate in DKA with pH values  $<6.9$  have been reported. Given that severe acidosis may lead to a myriad of adverse vascular effects, adult patients with a pH  $<6.9$  should receive 100 mmol sodium bicarbonate (two ampules) in 400 ml sterile water (an isotonic solution) with 20 mEq KCl administered at a rate of 200 ml/hours for 2 hours until the venous pH is  $>7.0$ . Bicarbonate as well as insulin therapy lowers serum potassium; therefore, potassium supplementation should be maintained in 'the intravenous fluid as described above and carefully monitored. Thereafter, venous pH should be assessed every 2 h until the pH rises to 7.0, and treatment should be repeated every 2 hours if necessary.<sup>12</sup>

### **Phosphate**

Despite whole body phosphate deficits in DKA that average 1.0 mmol/kg/body wt, serum phosphate is often normal or increased at presentation. Phosphate concentration decreases with insulin therapy.<sup>13</sup> Prospective randomized studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome in DKA, and overzealous phosphate therapy can cause severe hypocalcemia. Therefore, the routine use of phosphate in the treatment of DKA has resulted in no clinical benefit to the patient. However, to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with a serum phosphate concentration  $<1.0$  mg/dl. When needed, 20-30 mEq/l potassium phosphate can be added to replacement fluids.

## **COMPLICATIONS**

### **Hypoglycemia**

The two most common complications associated with the treatment of DKA in adult subjects are hypoglycemia and hypokalemia. Despite the use of low-dose insulin protocols, hypoglycemia is reported in 10 to 25% of patients during insulin therapy. Hypoglycemic events most commonly occur after several hours of insulin infusion (between 8 and 16 hours). The failure to reduce the insulin infusion rate and the failure to use dextrose containing solutions when blood glucose levels reach 250 mg/dL are the two most common causes of hypoglycemia during insulin therapy. Frequent blood glucose monitoring (every 1 to 2 hours) is mandatory for recognizing hypoglycemia because many patients with DKA who develop hypoglycemia during treatment do

not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger, and tachycardia.<sup>3</sup>

### **Hypokalemia**

Both insulin therapy and correction of acidosis decrease serum potassium levels by stimulating cellular potassium uptake in peripheral tissues and can lead to hypokalemia. The use of a low-dose insulin protocol and aggressive potassium replacement early in the management minimize the risk of hypokalemia.

### **Relapse**

Relapse of DKA can occur after sudden interruption of IV insulin therapy, in patients not given concomitant subcutaneous insulin, or with lack of frequent monitoring. To prevent recurrence of ketoacidosis during the transition period to subcutaneous insulin, it is important to allow an overlap of 1 to 2 hours between administration of subcutaneous regular insulin and discontinuation of intravenous insulin.

### **Others**

Other complications of diabetes include hyperchloremic acidosis with excessive use of NaCl or KCl resulting in a nonanion-gap metabolic acidosis. This acidosis has no adverse clinical effects and is gradually corrected over the subsequent 24 to 48 hours by enhanced renal acid excretion. The development of hyperchloremia can be prevented by reducing the chloride load with judicious use of hydration solutions.

### **Cerebral Edema**

Cerebral edema occurs in about 0.3 to 1% of all episodes of DKA, and its etiology, pathophysiology, and ideal method of treatment are poorly understood. Cerebral edema is more common in children, is associated with a mortality rate of 20 to 40%, and accounts for 57 to 87% of all DKA deaths in children. Cerebral edema is rarely reported in adult patients with DKA. Symptoms and signs of cerebral edema are variable and include onset of headache, gradual deterioration in level of consciousness, seizures, sphincter incontinence, pupil changes, papilledema, bradycardia, elevated blood pressure, and respiratory arrest. Cerebral edema typically occurs 4 to 12 hours after treatment is activated, but it can be present before treatment has begun or can develop any time during treatment for DKA. Treatment should be initiated as soon as the condition is suspected. The rate of fluid administration should be reduced and the patient should be transferred to the ICU for administration of mannitol and possibly mechanical ventilation. Intravenous mannitol should be given (0.25 to 1.0 g/kg over 20 minutes) in patients with signs of cerebral edema before they manifest respiratory failure. Hyper-tonic saline (3%) 5 to 10 mL/kg over 30 minutes may be an alternative to mannitol. There are no data regarding glucocorticoid use in DKA-related cerebral edema.<sup>14</sup>

### **PREVENTION**

Many cases of DKA can be prevented by better access to medical care, proper education, and effective communication with a health care provider during an intercurrent illness. Stopping insulin for economic reasons is a common precipitant of DKA. Sick-day management should be reviewed periodically with all patients. It should include specific information on (1) when to contact the health care provider, (2) blood glucose goals and the use of supplemental shorter rapid-acting insulin during illness, (3) means to suppress fever and treat infection, and (4) initiation of an easily digestible liquid diet containing carbohydrates and salt. Most importantly, the patient should be advised to never discontinue insulin and to seek professional advice early

in the course of the illness. Successful sick-day management depends on involvement by the patient and/or a family member. The patient/family member must be able to accurately measure and record blood glucose, urine, or blood ketone determination when blood glucose is > 300 mg/dl; insulin administered; temperature; respiratory and pulse rates; and body weight, and must be able to communicate all of this to a health care professional.

## **HYPERGLYCEMIC HYPEROSMOLAR SYNDROME**

Hyperglycemic hyperosmolar syndrome (HHS) is a serious complication of diabetes and has a high mortality rate. HHS is less common than DKA and accounts for 0.05% of all diabetes-related admissions. Mortality attributed to HHS is considerably higher than in DKA. Recent mortality rates are 5 to 25%, and the higher rates are most likely secondary to the underlying illnesses in an older patient population. HHS occurs most commonly in older patients with type 2 diabetes, but it can be seen in younger and type 1 patients as well. The typical patient with HHS has undiagnosed diabetes, is between 55 and 70 years of age, and is often a nursing home resident with associated comorbid conditions (stroke, renal failure). Up to 20% of patients admitted with HHS do not have a previous diagnosis of diabetes.

### **Causes**

The most common precipitating causes are pneumonia and urinary tract infection, accounting for 30 to 50% of cases. Other acute medical problems as precipitating causes include acute coronary syndromes, trauma, surgery, and cerebrovascular accidents that provoke the release of counter regulatory hormones or compromise access to water. Certain medications that cause DKA can also precipitate HHS, including glucocorticoids, thiazide diuretics, phenytoin, and  $\beta$ -blockers.<sup>3</sup>

### **Clinical Features**

HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. The diagnostic criteria for HHS (Table 3) include plasma glucose concentration greater than 600 mg/dL, serum osmolality greater than 320 mOsm/kg, and absence of ketoacidosis (pH > 7.3, serum bicarbonate > 18 mEq/L, and negative or minimal ketonemia and ketonuria). Altered sensorium (lethargy, stupor, coma) is common and correlates better with hyperosmolality than with the patient's age or with severity of the acid-base disturbance. Several reports have shown that the mean serum osmolality in patients who present with coma is greater than 340 mOsm/kg. Approximately 50% of patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis or an increase in serum lactate levels. BUN and creatinine levels are usually elevated and initial azotemia may be due to both pre-renal and renal causes. As with DKA, HHS is characterized by insulinopenia and increased circulating counter regulatory hormones. Higher levels of circulating insulin and lower levels of counter regulatory hormones in patients with HHS might explain the absent or minimal ketosis, which is the key difference from DKA.<sup>3</sup>

### **Treatment**

Therapeutic measures for HHS are similar to those recommended for patients with DKA. In general, treatment of HHS should be directed at replacing volume deficit, correcting hyperosmolality and electrolyte disturbances, and managing the underlying illness that may have precipitated metabolic decompensation. Patients with HHS may be severely dehydrated, with an average fluid deficit of 8 to 10 liters. Aggressive fluid replacement with normal saline at a rate of 500 to 1000 mL per hour for the first 2 to 3 hours is the usual recommendation, followed by 0.45% saline at a rate of 200 to 500 mL per hour.



Insulin treatment does not have to be aggressive if fluid replacement is vigorously pursued. Insulin is administered by an initial bolus of 0.1 U/kg followed by a continuous intravenous infusion calculated to deliver 0.1 U/kg per hour, and continued at this rate until blood glucose has decreased to approximately 250 to 300 mg/dL. At this time, intravenous fluids should be changed to dextrose-containing solutions (5%) and the insulin dose should be decreased by 50% (0.05 units/kg per hour), or to 2 to 3 units per hour. Thereafter, the rate of insulin administration is adjusted to maintain a blood glucose level of approximately 200 mg/dL. Intravenous insulin infusion is usually continued until the patient is hemodynamically stable, the level of consciousness is improved, and the patient is able to tolerate food. Although most patients require insulin therapy after recovery from HHS, some patients can be managed with diet alone or diet plus an oral hypoglycemic agent during the initial admission or shortly after presentation.

Increased serum potassium is commonly found in patients with HHS despite severe total body potassium depletion. Hyperglycemia and hyperosmolality cause a shift of potassium from the intracellular compartment into plasma, and they can contribute to a false estimate of total body potassium. The serum potassium deficit in patients with HHS is estimated at about 4 to 6 mEq/kg of body weight. The principles of potassium replacement in HHS are the same as in DKA.

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## Multiple Choice Questions

- 1. Precipitating causes of diabetic ketoacidosis include:**
    - A. Infections
    - B. Psychological stress
    - C. Non-compliance with therapy
    - D. All of above
  - 2. Ketoacidosis results from:**
    - A. Insulin deficiency
    - B. Excess counter-regulatory hormones
    - C. Elevation of proinflammatory cytokines
    - D. All of above
  - 3. Diagnostic criteria of DKA includes:**
    - A. B.glucose >250 mg/dl, S.Bicarbonates <15 mEq/L and pH <7.3
    - B. B.glucose >300 mg/dl, S.Bicarbonates >18 mEq/L and pH <7.5
    - C. B.glucose >350 mg/dl, S.Bicarbonates <20 mEq/L and pH <7.7
    - D. B.glucose >400 mg/dl, S.Bicarbonates >20 mEq/L and pH <7.8
  - 4. Complications of DKA do not include:**
    - A. Hypokalemia
    - B. Hypoglycemia
    - C. Cerebral edema
    - D. Myocardial infarction
  - 5. Diagnostic criteria of hyperosmolar hyperglycemic syndrome includes:**
    - A. B.glucose >400 mg/dl and S.osmolality >350
    - B. B.glucose >300 mg/dl and S.osmolality >400
    - C. B.glucose >600 mg/dl and S.osmolality >300
    - D. B.glucose >500 mg/dl and S.osmolality >360
  - 6. Onset of hypoglycemia in healthy subjects occurs at:**
    - A. Plasma glucose between 30-40 mg/dl
    - B. Plasma glucose between 49-58 mg/dl
    - C. Plasma glucose between 60-70 mg/dl
    - D. Plasma glucose between 70-80 mg/dl
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1. D 2. D 3. A 4. D 5. C 6. D