Hyperglycemic Crisis in Adults: Pathophysiology, Presentation, Pitfalls, and Prevention

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Editor's note: *This article is the 9th in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the* Clinical Diabetes *website (http://clinical.diabetesjournals.org).*

The patients never stop making water and the flow is incessant . . . . Life is short, unpleasant and painful, thirst unquenchable, drinking excessive . . . . If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up: the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire.

—Areteus, 3rd century[1]

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are acute and potentially life-threatening complications of diabetes. Although they have important differences, they both occur because of lack of insulin effect and can be considered two manifestations of the same underlying mechanism: insulin deficiency. Typically, patients with type 1 diabetes are more likely to exhibit DKA because of their absolute insulin deficiency, and patients with type 2 diabetes are more likely to experience HHS because of the presence of some insulin secretion. However, a significant number of patients stray from these patterns.[2–4]

Both of these conditions carry significant likelihood of morbidity and mortality, including cerebral edema, permanent neurological injury, and death. In large centers, the mortality rate for DKA is < 5%. However, the mortality rate for HHS is ~ 11%.[4] With the potential for mortality and an incidence of ~ 100,000 cases of DKA per year, general physicians and physicians in training will be treating patients with these acute complications of diabetes not infrequently. It is important to be familiar with the pathophysiology, presentation, treatment, complications, and—perhaps most importantly—prevention of DKA and HHS.

Pathophysiology

The basic cause of DKA and HHS is insufficient insulin effect. Combined with the insufficiency of insulin effect, there is an increase in counterregulatory hormone levels, including glucagon, cortsol, catecholamines, and growth hormone. Both factors contribute to hyperglycemia.

DKA and HHS may also be thought of as occurring on a spectrum of disease manifestation. On one end of the spectrum lie absolute insulin deficiency and profound ketosis and acidosis, which is DKA. DKA tends to occur in patients with type 1 diabetes, who, because of destruction of β-cells, exhibit absolute insulin deficiency. On the other end of the spectrum is extreme hyperglycemia without ketosis and acidosis.[4] This tends to occur in patients with type 2 diabetes who still produce enough endogenous insulin to suppress ketosis but not enough to control hyperglycemia. As the analogy implies, patients may present with various manifestations of both disorders. For example, a patient with DKA may have used enough insulin to partially suppress ketosis but still manifest profound hyperglycemia. Patients with HHS may also have varying degrees of ketosis and mild acidosis, depending on the degree to which they have been able to produce insulin and the extent of associated factors such as dehydration.[2–5]

Insulin deficiency causes a lack of glucose utilization in insulin-dependent tissues such as muscle and adipose and therefore leads to hyperglycemia. Lack of insulin also stimulates hyperglycemia by increasing hepatic gluconeogenesis. This is a common mechanism in both DKA and HHS.

Deprived of glucose utilization, the body must look elsewhere for fuel to survive. In addition to hyperglycemia, lack of insulin increases degradation of triglycerides into free fatty acids in adipose tissue, which travel to the liver and are converted to the ketoacids β-hydroxybutyric acid, acetone, and acetoacetate. Unopposed conterregulatory hormone effect causes further increases in glucose production from the liver

and degradation of triglycerides. The surge of ketoacid formation from unrestrained ketone body formation can be profound. DKA develops when the surge of ketoacid production is so powerful that a metabolic acidosis results. In HHS, there remains sufficient insulin presence to suppress ketosis enough to prevent the development of metabolic acidosis.[4]

Dehydration is another common finding in DKA and HHS. Glycosuria results when the blood glucose level exceeds the renal threshold (~ 180 mg/dl). Because of osmotic pressure, unregulated diuresis follows. Patients frequently complain of preceding polyuria and polydipsia. Considerable electrolyte loss may result, especially potassium depletion. Further dehydration and volume contraction can lead to worsening of hyperglycemia.[2–4]

Presentation

Patients presenting in HHS and DKA typically exhibit a history of polyuria and polydipsia. Frequently, one can identify a precipitating factor leading to DKA. Such factors can include inappropriate use of insulin (noncompliance), cardiovascular disease, or infection, which may be the most common causes of DKA.[5] Patients presenting with acute hyperglycemia should undergo review of medications and insulin administration as well as an infection evaluation with chest X-ray, blood cultures, urinalysis, foot inspection, and other infection evaluation as clinically warranted. Patients with DKA may also manifest leukocytosis simply due to DKA. However, leukocytosis > 25,000 may be indicative of underlying or precipitating infection.[4]

It is important to not overlook other possible causes of DKA and HHS, however. Myocardial infarction may precipitate hyperglycemia and DKA via an increase in counterregulatory hormones, such as epinephrine. Because silent ischemia may occur in up to one in five type 2 diabetic patients > 50 years of age, the threshold for ischemia evaluation should be low.[6] Cerebrovascular accidents may also precipitate similar counterregulatory response.

Drugs such as thiazides, sympathomimetics, second-generation antipsychotics, and corticosteroids may also precipitate HHS and DKA. Other disorders that may precipitate diabetes include pancreatitis and illicit drug use.[4] In women of reproductive age, clinicians should consider screening for pregnancy, which has been associated with the onset of DKA.[7]

Additionally, and especially in patients with type 1 diabetes, decline in diabetes control and hyperglycemia may indicate the onset of an autoimmune thyroid disease, such as Grave's disease or Hashitoxicosis.[8–10] Patients exhibiting signs of thyroid dysfunction such as unexplained weight loss, heat intolerance, exophthalmos, or other concerning symptoms should be screened for thyroid dysfunction.

Patients may develop progressive hyperglycemia over weeks or days, although patients with DKA may experience more rapid onset than those with HHS. Symptoms of both HHS and DKA include polyuria and polydipsia due to hyperglycemia and signs of dehydration, including lack of skin turgor, hypotension, dry oral mucosae, tachycardia, weakness, and altered sensorium. Patients with DKA typically exhibit signs of acidosis, such as abdominal pain (sometimes severe), nausea, vomiting, and Kussmaul respirations, and may also exhibit guaiac-positive vomitus. Hypothermia, should it be present, is a poor prognostic indicator.[4]

Laboratory findings in patients with DKA include hyperglycemia, ketosis, and metabolic acidosis. Patients who are suspected of DKA or HHS should undergo measurement of electrolytes with anion gap, glucose (serological), creatinine and blood urea nitrogen, serum ketones, urinalysis with ketones, complete blood count, A1C, and arterial blood gas testing. Additionally, electrocardiogram, chest X-ray, and urine, sputum, and blood cultures may be warranted.[4] In children, the most common cause of DKA is omission of insulin. If children are otherwise healthy and there are no signs of infection, it may be acceptable to omit an infection workup.[5]

Diagnostic criteria for DKA include blood glucose > 250 mg/dl, arterial pH < 7.3, serum bicarbonate < 15 mEq/l, and moderate degrees of ketonemia or ketonuria. Significant ketosis has been shown in up to one-third of patients with HHS, again indicative of the continuum of pathology between DKA and HHS.[5]

Buildup of ketoacids is responsible for anion gap metabolic acidosis in DKA. It is important, however, to remember other causes of anion gap metabolic acidoses, including starvation, lactic acidosis (especially in patients using metformin), salicylates, ethanol, methanol, ethylene glycol, paraldehyde, renal insufficiency, and isopropyl alcohol intoxication.

Serum potassium levels are typically elevated in response to the presence of acidosis and insulin deficiency, but total body potassium is depleted. Patients presenting with hypokalemia in the setting of DKA are particularly potassium-depleted and require aggressive monitoring and potassium repletion. Both amylase and lipase may be elevated in the setting of DKA and are not necessarily indicative of pancreatitis.[4,5]

Treatment

The cornerstones of treatment of DKA and HHS are fluids, insulin, correction of electrolyte abnormalities, and close monitoring. In the absence of underlying renal and cardiac disease, initial fluid resuscitation should consist of isotonic fluids to restore renal perfusion. Typical initial infusion rates are 15–20 ml/kg body weight/hour during the first hour. Subsequently, fluids may be altered or titrated based on degree of dehydration and electrolyte abnormalities. Commonly, hypotonic fluids are infused at 4–14 ml/kg/hour after the initial fluid bolus. Titration of fluids is based on hemodynamic improvement, urine output, laboratory improvement, and clinical response. Patients with underlying cardiac and renal disease may require lower initial fluid resuscitation rates and more frequent monitoring of clinical status to avoid fluid overload.[4,5]

Insulin therapy for DKA and HHS is typically administered intravenously, although uncomplicated mild to moderate DKA may be managed with subcutaneous insulin therapy. Typically, in the absence of hypokalemia, patients receive a bolus of intravenous regular insulin at 0.1 units/kg body weight and a subsequent infusion of 0.1 units/kg body weight/hour. Doses may be titrated based on clinical response, which will vary based on the degree of insulin resistance. For example, patients with type 2 diabetes who present in DKA will typically require a higher dose of insulin than those with type 1 diabetes because of higher insulin resistance.

Insulin infusion is typically adjusted to achieve a glucose drop of 50–75 mg/dl per hour. Insulin infusion may be decreased when the glucose level approaches 200 mg/dl in DKA or 300 mg/dl in HHS, at which time dextrose may be added to the fluids and insulin infusion continued at a lower rate to maintain the glucose values until acidosis has resolved in DKA or mental changes and hyperosmolarity have resolved in HHS.[4,5]

If subcutaneous insulin is to be used to treat uncomplicated DKA, patients typically receive an initial dose of 0.2 units/kg followed by 0.1 units/kg every hour or an initial dose of 0.3 units/kg and subsequently 0.2 units/kg every 2 hours while blood gluose remains > 250 mg/dl. When glucose levels fall to < 250 mg/dl, the insulin dose may be decreased by half and administered every 1 or 2 hours until resolution of DKA. Such approaches may be associated with a lower cost of hospitalization by avoiding intensive care unit placement.[4,11,12]

Electrolytes, glucose, blood urea nitrogen, osmolality, creatinine, and pH (arterial or venous) should be drawn every 2–4 hours to monitor patients' responses to therapy and to allow titration of insulin and fluids. It is important to note that hyperglycemia typically resolves before ketosis; therefore, dextrose should be added to fluids as glucose declines (as described above).

Ketosis should be measured via β-hydroxybutyric acid whenever possible because that is the prevalent ketone body produced in DKA. The nitroprusside reaction, which is still used in many laboratories to detect ketone formation, does not detect β-hyrdoxybutyric acid and therefore may yield false-negative results.[4]

Most patients presenting in DKA exhibit hyperkalemia as a result of insulin deficiency and acidosis despite total body potassium depletion. Treatment with insulin, restoration of normal circulatory volume, and resolution of acidosis allow total body potassium depletion to manifest itself as hypokalemia during treatment of DKA.

In the setting of normal renal function, potassium should be added to fluids when serum potassium falls to < 5.3 mEq/l. Including 20–30 mEq of potassium in each liter of fluid is usually sufficient to maintain a potassium concentration within normal limits. In patients with DKA presenting with hypokalemia, potassium repletion should begin at once, and insulin therapy should be initiated when potassium concentration is restored to > 3.3 mEq/l. This will help to avoid cardiac arrhythmia and skeletal muscle dysfunction because insulin initiation can cause an acute decline in serum potassium concentration.

Use of bicarbonate to raise pH is controversial. Although it helps correct acidosis, it may be associated with a higher risk of cerebral edema in patients with a pH > 7.0. Its use, therefore, is not recommended in patients with an arterial pH > 7.0.

Patients also frequently exhibit hypophosphatemia at presentation in DKA, but phosphate repletion has not demonstrated a beneficial effect on clinical outcomes in DKA.[13] Because of the increased risk of cardiac and skeletal muscle dysfunction in hypophosphatemia, it may be prudent to administer 20–30 mEq/l of potassium phosphate in patients with cardiac disease, anemia, or respiratory depression or with profound hypophosphatemia (> 1.0 mg/dl). Patients receiving phosphate therapy should be monitored closely for hypocalcemia, which can result from phosphate administration.[5,13]

Resolution of diabetic ketoacidosis is marked by a glucose level < 200 mg/dl, serum bicarbonate > 18 mEq/l, and venous pH > 7.3. Patients should resume rapid-acting insulin at meals and intermediate- or long-acting insulin when they are able to eat substantial carbohydrate. It is important to continue intravenous insulin for several hours after

resumption of subcutaneous insulin to avoid recurrent hyperglycemia and a possible return to ketosis.

Pitfalls

The most common complications that occur when treating adults with ketoacidosis are hypokalemia and hypoglycemia. Potassium depletion is the most life-threatening electrolyte abnormality in the treatment of DKA. As previously described, total body potassium at presentation in DKA is low despite hyperkalemia because of metabolic acidosis. Delayed potassium supplementation can lead to considerable hypokalemia as the serum potassium concentration drops precipitously in the presence of insulin and resolution of ketoacidosis.[5,14] Severe hypokalemia can lead to neuromuscular dysfunction, cardiac arrhythmia, and potentially death. In the setting of normal renal function, patients should receive potassium supplementation in their fluids when the potassium level approaches normal values.[4]

Hypoglycemia is also a potential complication of DKA. Use of supplemental dextrose when glucose levels approach 250 mg/dl may help prevent hypoglycemia. The threat of hypokalemia and hypoglycemia both also illustrate the importance of frequent reassessment of patients treated for DKA.

Care must also be taken in intravenous fluid administration. Patients with underlying medical conditions such as renal insufficiency or congestive heart failure are susceptible to fluid overload. Patients should be assessed for such disorders before initiation of fluid resuscitation.

Cerebral edema is yet another potential complication of DKA and HHS. It occurs more frequently in pediatric patients than in adults. It may occur in as many as 1% of children with DKA.[4,5,15] The precise mechanism of cerebral edema is not clear, and it may occur by different mechanisms in different patients. Signs of cerebral edema include mental status changes, vomiting, headache, lethargy, elevated diastolic blood pressure, decorticate or decerebrate posturing, cranial nerve palsies, or Cheyne-Stokes respiration. Treatment options include use of mannitol or hypertonic saline to decrease cerebral edema, although there have been no large controlled trials clearly demonstrating benefit.[15]

Hyperchloremic nonanion gap metabolic acidosis is a very frequent finding after resolution of DKA. It may occur because of the loss of ketoanions during DKA and is exacerbated by supplementation with supraphysiological levels of chloride in normal saline. The extent of hyperchloremic metabolic acidosis may be lessened by limiting the amount of chloride administered during treatment, but it is important to note that this finding is self-limiting and not associated with adverse clinical outcomes.[4,5]

Prevention

Prevention of DKA and HHS is targeted toward treatable precipitating factors. Because infection is a frequent cause of DKA and HHS, patients should be instructed to monitor glucose closely should they develop early symptoms of infection such as cough, fever, nausea, or wounds. Patients should also be educated regarding foot care, especially in the setting of peripheral sensory neuropathy, which may predispose to infection. Should symptoms develop, patients should monitor glucose closely and take extra precautions such as administering correction doses of insulin and maintaining adequate hydration in the setting of hyperglycemia-induced diuresis. Sick-day education should also include instructions to avoid prolonged fasting and to never discontinue insulin therapy. If patients do not administer their own insulin or medications, their caregivers should receive similar instructions as to proper treatment of hyperglycemia and infection.

In addition to infection, DKA and HHS are also frequently associated with incorrect use of or omission of insulin. Careful education regarding the proper use and dosing of insulin at routine visits may help reduce the recurrence of DKA. Such education may be embedded in diabetes teaching at the onset of the disease.

Patients who experience recurrent DKA may also omit insulin or administer incorrect amounts of insulin because of socioeconomic factors, lack of knowledge regarding insulin dosing, or behavioral reasons.[5] Glycemic control may also be related to numeracy and literacy skills.[16,17] Careful discussion of insulin dosing, injection technique, financial status, and level of education at disease onset or before hospital discharge may help prevent recurrent episodes of DKA or HHS.

DKA and HHS are both life-threatening disorders that carry significant risk of morbidity and mortality. Physicians caring for diabetic patients in the inpatient setting or working in emergent care will likely treat significant numbers of patients with DKA and HHS. Fortunately, most patients recover uneventfully. Care must be taken, however, to not approach treatment of DKA and HHS as "routine," because rare complications such as cerebral edema can be fatal. Careful attention to proper treatment and early identification of the underlying causes of hyperglycemia will allow for the most rapid patient recovery and lowest risk of morbidity and mortality. Detailed patient education and instruction regarding outpatient care may help prevent

initial occurrences or the recurrence of DKA or HHS.

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