Diabetic Ketoacidosis

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Practice Essentials

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes that mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes. This condition is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria.

Signs and symptoms

The most common early symptoms of DKA are the insidious increase in polydipsia and polyuria. The following are other signs and symptoms of DKA:

- Malaise, generalized weakness, and fatigability
- Nausea and vomiting; may be associated with diffuse abdominal pain, decreased appetite, and anorexia
- Rapid weight loss in patients newly diagnosed with type 1 diabetes
- History of failure to comply with insulin therapy or missed insulin injections due to vomiting or psychological reasons or history of mechanical failure of insulin infusion pump
- Decreased perspiration
- Altered consciousness (eg, mild disorientation, confusion); frank coma is uncommon but may occur when the condition is neglected or with severe dehydration/acidosis

Signs and symptoms of DKA associated with possible intercurrent infection are as follows:

- Fever
- Coughing
- Chills
- Chest pain
- Dyspnea
- Arthralgia

See Clinical Presentation for more detail.

Diagnosis

On examination, general findings of DKA may include the following:

- Ill appearance
- Dry skin
- Labored respiration
- Dry mucous membranes
- Decreased skin turgor
- Decreased reflexes
- Characteristic acetone (ketotic) breath odor
- Tachycardia
- Hypotension
- Tachypnea
- Hypothermia

In addition, evaluate patients for signs of possible intercurrent illnesses such as MI, UTI, pneumonia, and perinephric abscess. Search for signs of infection is mandatory in all cases.

Testing

Initial and repeat laboratory studies for patients with DKA include the following:

- Serum glucose levels
- Serum electrolyte levels (eg, potassium, sodium, chloride, magnesium, calcium, phosphorus)
- Bicarbonate levels
- Amylase and lipase levels
- Urine dipstick
- Ketone levels
- Serum or capillary beta-hydroxybutyrate levels
- ABG measurements
- CBC count
- BUN and creatinine levels
- Urine and blood cultures if intercurrent infection is suspected
- ECG (or telemetry in patients with comorbidities)

Note that high serum glucose levels may lead to dilutional hyponatremia; high triglyceride levels may lead to factitious low glucose levels; and high levels of ketone bodies may lead to factitious elevation of creatinine levels.

Imaging tests

Radiologic studies that may be helpful in patients with DKA include the following:

- Chest radiography: To rule out pulmonary infection such as pneumonia
- Head CT scanning: To detect early cerebral edema; use low threshold in children with DKA and altered mental status
- Head MRI: To detect early cerebral edema (order only if altered consciousness is present [1])

Do not delay administration of hypertonic saline or mannitol in those pediatric cases where cerebral edema is suspected, as many changes may be seen late on head imaging.

See Workup for more detail.

Management

Goals

Treatment of ketoacidosis should aim for the following:

- Fluid resuscitation
- Reversal of the acidosis and ketosis
- Reduction in the plasma glucose concentration to normal
- Replenishment of electrolyte and volume losses
- Identification the underlying cause

Pharmacotherapy

Regular and analog human insulins[2] are used for correction of hyperglycemia, unless bovine or pork insulin is the only available insulin.

Medications used in the management of DKA include the following:

- Rapid-acting insulins (eg, insulin aspart, insulin glulisine, insulin lispro)
- Short-acting insulins (eg, regular insulin)
- Electrolyte supplements (eg, potassium chloride)
- Alkalinizing agents (eg, sodium bicarbonate)

See Treatment and Medication for more detail.

Background

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes. DKA mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes (most likely latent autoimmune diabetes of adults [LADA] or Flatbush diabetes).

DKA is a state of absolute or relative insulin deficiency aggravated by ensuing hyperglycemia, dehydration, and acidosis-producing derangements in intermediary metabolism. The most common causes are underlying infection, disruption of insulin treatment, and new onset of diabetes. (See Etiology.)

DKA is defined clinically as an acute state of severe uncontrolled diabetes associated with ketoacidosis that requires emergency treatment with insulin and intravenous fluids. (See Treatment and Management and Medications.)

Biochemically, DKA is defined as an increase in the serum concentration of ketones greater than 5 mEq/L, a blood glucose level greater than 250 mg/dL (although it is usually much higher), and a blood (usually arterial) pH less than 7.3. Ketonemia and ketonuria are characteristic, as is a serum bicarbonate level of 18 mEq/L or less (less than 5 mEq/L is indicative of severe DKA). These biochemical changes are frequently associated with increased anion gap, increased serum osmolarity and increased serum uric acid. (See Clinical Presentation.)

Herrington et al collected simultaneous arterial and venous samples from 206 critically ill patients and analyzed in duplicate.[3] They calculated coefficients of variation and 95% limits of agreement for arterial and venous samples and constructed statistical plots to assess the degree of agreement between samples. They found that coefficients of variation for arterial and venous samples were similar for pH, serum bicarbonate, and potassium, indicating that both are sufficiently reliable for the management of critically ill patients, particularly those with DKA.

Mental status changes can be seen with mild-to-moderate DKA; more severe deterioration in mental status is typical with moderate-to-severe DKA.

See Diabetes Mellitus, Type 1 and Diabetes Mellitus, Type 2 for more complete information on these topics.

Pathophysiology

Diabetic ketoacidosis (DKA) is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria. DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones (ie, glucagon, cortisol, growth hormone, epinephrine). This type of hormonal imbalance enhances hepatic gluconeogenesis, glycogenolysis, and lipolysis.

Hepatic gluconeogenesis, glycogenolysis secondary to insulin deficiency, and counter-regulatory hormone excess result in severe hyperglycemia, while lipolysis increases serum free fatty acids. Hepatic metabolism of free fatty acids as an alternative energy source (ie, ketogenesis) results in accumulation of acidic intermediate and end metabolites (ie, ketones, ketoacids). Ketone bodies have generally included acetone, beta-hydroxybutyrate, and acetoacetate. It should be noted, however, that only acetone is a true ketone, while acetoacetic acid is true ketoacid and beta-hydroxybutyrate is a hydroxy acid.

Meanwhile, increased proteolysis and decreased protein synthesis as result of insulin deficiency add more gluconeogenic substrates to the gluconeogenesis process. In addition, the decreased glucose uptake by peripheral tissues due to insulin deficiency and increased counter regulatory hormones increases hyperglycemia.

Ketone bodies are produced from acetyl coenzyme A mainly in the mitochondria within hepatocytes when carbohydrate utilization is impaired because of relative or absolute insulin deficiency, such that energy must be obtained from fatty acid metabolism. High levels of acetyl coenzyme A present in the cell inhibit the pyruvate dehydrogenase complex, but pyruvate carboxylase is activated. Thus, the oxaloacetate generated enters gluconeogenesis rather than the citric acid cycle, as the latter is also inhibited by the elevated level of nicotinamide adenine dinucleotide (NADH) resulting from excessive beta-oxidation of fatty acids, another consequence of insulin resistance/insulin deficiency. The excess acetyl coenzyme A is therefore rerouted to ketogenesis.

Progressive rise of blood concentration of these acidic organic substances initially leads to a state of ketonemia,

although extracellular and intracellular body buffers can limit ketonemia in its early stages, as reflected by a normal arterial pH associated with a base deficit and a mild anion gap.

When the accumulated ketones exceed the body's capacity to extract them, they overflow into urine (ie, ketonuria). If the situation is not treated promptly, a greater accumulation of organic acids leads to frank clinical metabolic acidosis (ie, ketoacidosis), with a significant drop in pH and bicarbonate[4] serum levels. Respiratory compensation for this acidotic condition results in rapid shallow breathing (Kussmaul respirations).

Ketones/ketoacids/hydroxy acids, in particular, beta-hydroxybutyrate, induce nausea and vomiting that consequently aggravate fluid and electrolyte loss already existing in DKA. Moreover, acetone produces the fruity breath odor that is characteristic of ketotic patients.

Glucosuria leads to osmotic diuresis, dehydration and hyperosmolarity. Severe dehydration, if not properly compensated, may lead to impaired renal function. Hyperglycemia, osmotic diuresis, serum hyperosmolarity, and metabolic acidosis result in severe electrolyte disturbances. The most characteristic disturbance is total body potassium loss. This loss is not mirrored in serum potassium levels, which may be low, within the reference range, or even high.

Potassium loss is caused by a shift of potassium from the intracellular to the extracellular space in an exchange with hydrogen ions that accumulate extracellularly in acidosis. Much of the shifted extracellular potassium is lost in urine because of osmotic diuresis.

Patients with initial hypokalemia are considered to have severe and serious total body potassium depletion. High serum osmolarity also drives water from intracellular to extracellular space, causing dilutional hyponatremia. Sodium also is lost in the urine during the osmotic diuresis.

Typical overall electrolyte loss includes 200-500 mEq/L of potassium, 300-700 mEq/L of sodium, and 350-500 mEq/L of chloride. The combined effects of serum hyperosmolarity, dehydration, and acidosis result in increased osmolarity in brain cells that clinically manifests as an alteration in the level of consciousness.

Many of the underlying pathophysiologic disturbances in DKA are directly measurable by the clinician and need to be monitored throughout the course of treatment. Close attention to clinical laboratory data allows for tracking of the underlying acidosis and hyperglycemia, as well as prevention of common potentially lethal complications such as hypoglycemia, hyponatremia, and hypokalemia.

Hyperglycemia

The absence of insulin, the primary anabolic hormone, means that tissues such as muscle, fat, and liver do not uptake glucose. Counterregulatory hormones, such as glucagon, growth hormone, and catecholamines, enhance triglyceride breakdown into free fatty acids and gluconeogenesis, which is the main cause for the elevation in serum glucose level in DKA. Beta-oxidation of these free fatty acids leads to increased formation of ketone bodies.

Overall, metabolism in DKA shifts from the normal fed state characterized by carbohydrate metabolism to a starvation state characterized by fat metabolism.

Secondary consequences of the primary metabolic derangements in DKA include an ensuing metabolic acidosis as the ketone bodies produced by beta-oxidation of free fatty acids deplete extracellular and cellular acid buffers. The hyperglycemia-induced osmotic diuresis depletes sodium, potassium, phosphates, and water.

Hyperglycemia usually exceeds the renal threshold of glucose absorption and results in significant glucosuria. Consequently, water loss in the urine is increased due to osmotic diuresis induced by glucosuria. This incidence of increased water loss results in severe dehydration, thirst, tissue hypoperfusion, and, possibly, lactic acidosis, or renal impairment.

See Hyperosmolar Hyperglycemic State for more complete information on this topic.

Dehydration and electrolyte loss

Typical free water loss in DKA is approximately 6 liters or nearly 100 mL/kg of body weight. The initial half of this amount is derived from intracellular fluid and precedes signs of dehydration, while the other half is from extracellular fluid and is responsible for signs of dehydration.

Patients often are profoundly dehydrated and have a significantly depleted potassium level (as high as 5 mEq/kg body weight). A normal or even elevated serum potassium concentration may be seen due to the extracellular shift of potassium in acidotic conditions, and this very poorly reflects the patient's total potassium stores. The serum potassium concentration can drop precipitously once insulin treatment is started, so great care must be taken to repeatedly monitor serum potassium levels. Urinary loss of ketoanions with brisk diuresis and intact renal function also may lead to a component of hyperchloremic metabolic acidosis.

Etiology

The most common scenarios for diabetic ketoacidosis (DKA) are underlying or concomitant infection (40%), missed or disrupted insulin treatments (25%), and newly diagnosed, previously unknown diabetes (15%). Other associated causes make up roughly 20% in the various scenarios.

Causes of DKA in type 1 diabetes mellitus include the following:[5]

- In 25% of patients, DKA is present at diagnosis of type 1 diabetes due to acute insulin deficiency (occurs in 25% of patients)
- Poor compliance with insulin through the omission of insulin injections, due to lack of patient/guardian education or as a result of psychological stress, particularly in adolescents
- Missed, omitted or forgotten insulin doses due to illness, vomiting or excess alcohol intake
- Bacterial infection and intercurrent illness (eg, urinary tract infection [UTI])
- *Klebsiella pneumoniae* (the leading cause of bacterial infections precipitating DKA)
- Medical, surgical, or emotional stress
- Brittle diabetes
- Idiopathic (no identifiable cause)
- Insulin infusion catheter blockage
- Mechanical failure of the insulin infusion pump

Causes of DKA in type 2 diabetes mellitus include the following:[6]

- Intercurrent illness (eg, myocardial infarction, pneumonia, prostatitis, UTI)
- Medication (eg, corticosteroids, pentamidine, clozapine)

DKA also occurs in pregnant women, either with preexisting diabetes or with diabetes diagnosed during pregnancy. Physiologic changes unique to pregnancy provide a background for the development of DKA. DKA in pregnancy is a medical emergency, as mother and fetus are at risk for morbidity and mortality.

Epidemiology

Despite advancements in self-care of patients with diabetes, DKA accounts for 14% of all hospital admissions of patients with diabetes and 16% of all diabetes-related fatalities. Almost 50% of diabetes-related admissions in young persons are related to DKA. DKA frequently is observed during the diagnosis of type 1 diabetes and often indicates this diagnosis. While the exact incidence is not known, it is estimated to be 1 out of 2000.

DKA occurs primarily in patients with type 1 diabetes. The incidence is roughly 2 episodes per 100 patient years of diabetes, with about 3% of patients with type 1 diabetes initially presenting with DKA. It can occur in patients with type 2 diabetes as well; this is less common, however.

The incidence of diabetic ketoacidosis in developing countries is not known, but it may be higher than in industrialized nations.[7]

The incidence of DKA is higher in whites because of the higher incidence of type 1 diabetes in this racial group. The incidence of diabetic ketoacidosis (DKA) is slightly greater in females than in males for reasons that are unclear. Recurrent DKA frequently is seen in young women with type 1 diabetes and is caused mostly by the omission of insulin treatment.

Among persons with type 1 diabetes, DKA is much more common in young children and adolescents than it is in adults. DKA tends to occur in individuals younger than 19 years, but it may occur in patients with diabetes at any age.

Although multiple factors (eg, ethnic minority, lack of health insurance, lower body mass index, preceding infection, delayed treatment) affect the risk of developing DKA among children and young adults, intervention is possible between symptom onset and development of DKA.[8]

Prognosis

The overall mortality rate for DKA is 0.2-2%, with being at the highest of the range in developing countries. The presence of deep coma at the time of diagnosis, hypothermia, and oliguria are signs of poor prognosis.

The prognosis of properly treated patients with diabetic ketoacidosis is excellent, especially in younger patients if intercurrent infections are absent. The worst prognosis usually is observed in older patients with severe intercurrent illnesses (eg, myocardial infarction, sepsis, or pneumonia), especially when these patients are treated outside an intensive care unit.

When DKA is treated properly, it rarely produces residual effects. Before the discovery of insulin in 1922, the mortality rate was 100%. Over the last 3 decades, mortality rates from DKA have markedly decreased in developed countries, from 7.96% to 0.67%.[9]

A fetal mortality rate as high as 30% is associated with DKA. The rate is as high as 60% in diabetic ketoacidosis with coma. Fetal death typically occurs in women with overt diabetes, but it may occur with gestational diabetes. In children younger than 10 years, diabetic ketoacidosis causes 70% of diabetes-related fatalities.

The best results are observed in patients treated in intensive care units during the first 1-2 days of hospitalization, although some hospitals are successful in treating mild cases of DKA in the emergency room (ie, Emergency Valuable Approach and Diabetes Education [EVADE] protocol). A high mortality rate among nonhospitalized patients illustrates the necessity of early diagnosis and implementation of effective prevention programs.

Cerebral edema remains the most common cause of mortality, particularly in young children and adolescents.[1] Cerebral edema frequently results from rapid intracellular fluid shifts. Other causes of mortality include severe hypokalemia, adult respiratory distress syndrome, and comorbid states (eg, pneumonia, acute myocardial infarction).

A heightened understanding of the pathophysiology of DKA along with proper monitoring and correction of electrolytes has resulted in a significant reduction in the overall mortality rate from this life-threatening condition in most developed countries.

Patient Education

The introduction of diabetes educational programs in most diabetes clinics has contributed to a reduction in the occurrence of diabetic ketoacidosis (DKA) in patients with known diabetes. Such programs teach patients how to avoid DKA by self-testing for urinary ketones when their blood glucose is high or when they have unexplained nausea or vomiting and adjusting their insulin regimens on sick days.

It is essential to educate patients in the prevention of diabetic ketoacidosis (DKA) so that a recurrent episode can be avoided. Central to patient education programs for adults with diabetes is instruction on the self-management process and on how to handle the stress of intercurrent illness.[10, 11]

The patient education program needs to ensure that patients understand the importance of close and careful monitoring of blood glucose levels, particularly during infection, trauma, and other periods of stress.

For excellent patient education resources, visit eMedicineHealth's Diabetes Center. In addition, see eMedicineHealth's patient education article Diabetic Ketoacidosis.

Clinical Presentation

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