CE **Article #1 (1.5 contact hours)**
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FOCAL POINT

- Understanding the interplay of hormonal abnormalities is essential to the successful recognition of metabolic disorders associated with diabetic ketoacidosis (DKA).

KEY FACTS

- An increased glucagon:insulin ratio is the key hormonal abnormality precipitating DKA, p. 221.
- Stressful events such as infection or metabolic disease may cause a shift from diabetes mellitus to DKA, p. 221.
- Glucagon promotes hyperglycemia via glycogenolysis and gluconeogenesis and increases hepatic ketone production, p. 222.
- Cortisol, epinephrine, and growth hormone cause fat and muscle breakdown to increase substrate for glucose and ketone production, p. 223.
- The presence of hyperglycemia, glucosuria, ketonuria, and metabolic acidosis is helpful in establishing a diagnosis of DKA, p. 224.

Diabetic Ketoacidosis: Pathophysiology and Clinical and Laboratory Presentation

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ABSTRACT: Diabetic ketoacidosis (DKA) is a complex disease process with multiple hormonal abnormalities that cause various deleterious fluid and electrolyte changes in both animals and humans. Pathogenesis of DKA involves a relative excess ratio of glucagon to insulin. Other hormones influencing DKA include cortisol, epinephrine, and growth hormone. Abnormal physical examination and clinicopathologic findings result from these hormonal changes.

Diabetic ketoacidosis (DKA), a complex disease process that occurs in humans and animals with diabetes mellitus (DM), may cause severe illness on clinical presentation.[1,2] Successful diagnosis and rapid, appropriate therapy can be accomplished by understanding the pathogenesis as well as the fluid, electrolyte, and acid–base abnormalities that are an inherent part of this disease process.[2] Trained clinicians who provide rapid emergency therapy aimed at reversing the deleterious changes caused by underlying hormonal abnormalities can improve the outcome in these patients.[2] This article discusses the hormonal abnormalities leading to DKA, the systemic effects of these abnormalities, and the clinical manifestations of this disease. A companion article will discuss treatment recommendations for dogs and cats with DKA.

PATHOGENESIS

Insulin

The initiating event of DM, and subsequently DKA, is loss of insulin activity that causes intracellular glucose transfer to fail, leading to cellular starvation.[3] This can occur with absolute or relative lack of insulin production by pancreatic beta cells, loss or inactivity of insulin receptors at the cellular level, or through a combination of both events.[4] Insulin, which is produced by the pancreatic beta cells, promotes cellular uptake of glucose for energy by most cells in the body, especially muscle, adipose tissue, and liver.[4] In the absence of insulin, cells are not able to take up and use glucose for energy; therefore, hyperglycemia ensues.[5] Brain cells are unique in that they are permeable to glucose and can use it without the inter-

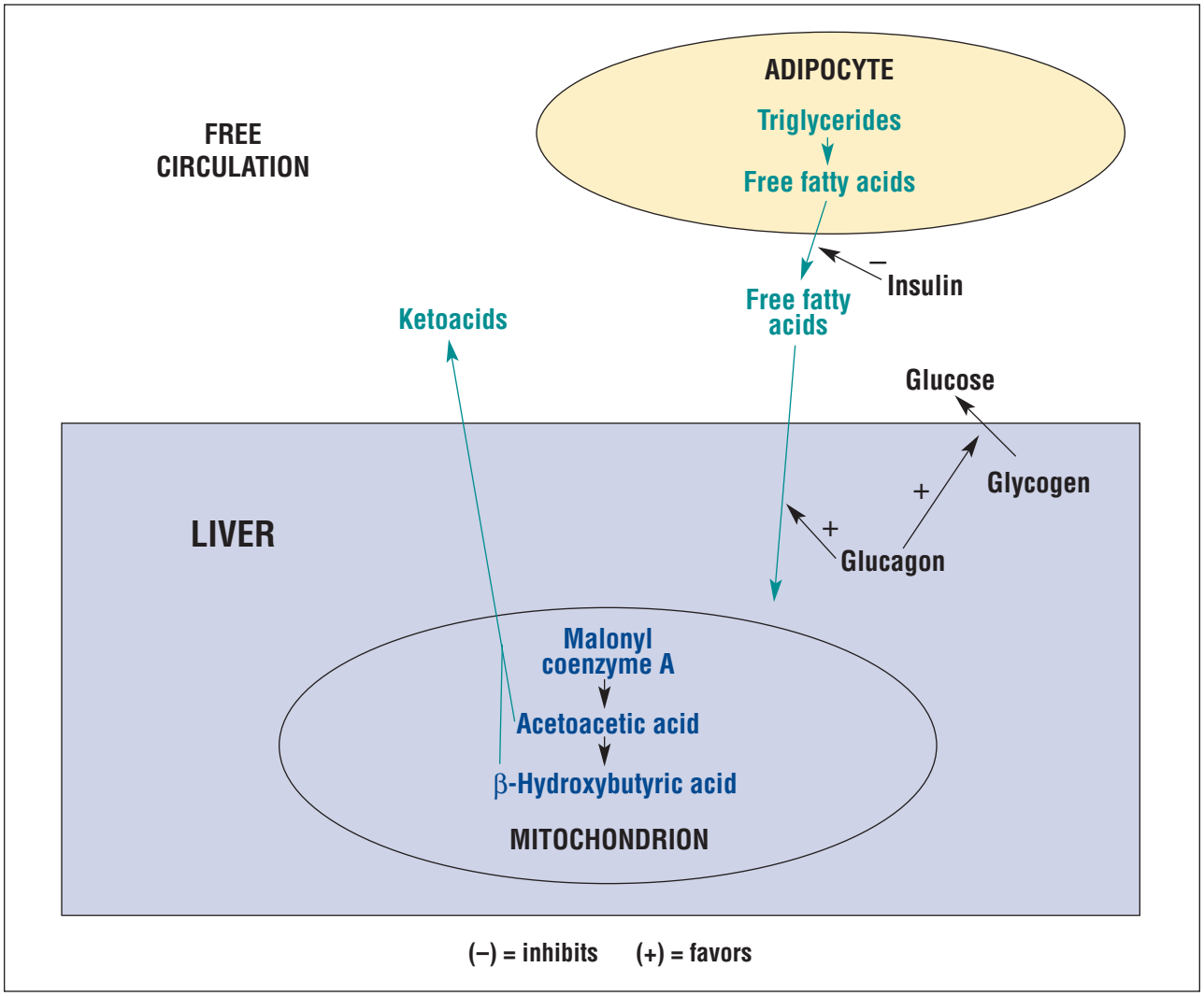

Figure 1—The effects of insulin and glucagon on adipocytes and hepatocytes cause lipolysis, ketoacid formation, glycogenolysis, and gluconeogenesis. Insulin inhibits lipolysis; therefore, without insulin, free fatty acids from the breakdown of triglycerides are released into circulation. Glucagon facilitates glycogenolysis and the formation of ketoacids (acetoacetate and β-hydroxybutyrate).

mediation of insulin.[4] Most cells in the body can use free fatty acids (FFAs) as an energy source in the absence of glucose. Cells that have an absolute requirement for glucose include the brain, retina, and germinal epithelium of the gonads.[4]

Insulin also retards lipolysis. Without insulin, adipocytes undergo lipolysis to release FFAs into circulation. Circulating FFAs are taken up by the liver for triglyceride (TG) production as well as for the manufacture of ketone bodies, which can become an additional energy source for most cells in the body (Figure 1). In uncomplicated DM, TG production predominates, and ketone production occurs slowly enough that the ketones can be used by tissues for energy and will not cause hyperketonemia.[6]

Abnormalities caused by lack of insulin activity explain the changes (e.g., hyperglycemia, tissue wasting) that occur with uncomplicated DM but do not fully explain the pathogenesis of DKA. A series of hormonal events take place in DM patients that make the transition to DKA, resulting in the deleterious fluid and electrolyte shifting and acidemia that occur with ketoacidosis.[7] Relative increase of glucagon, epinephrine, cortisol, and growth hormone occur compared with the decrease of appropriate insulin activity. An elevated glucagon:insulin ratio is characteristic of DKA.[1,2] This change is usually caused by a stressful event; however, the inciting event may not be identifiable in every patient.

Glucagon

Pancreatic alpha cells produce glucagon.[4] The purpose of glucagon is to promote ketogenesis and increase available cellular energy by increasing glucose production. Glucagon acts to raise blood glucose levels by promoting hepatic gluconeogenesis and glycogenolysis. In the absence of insulin, cellular demand for glucose stimulates the release of glucagon from the pancreas.[4]

Glucagon can raise blood glucose within minutes of release by stimulating hepatic glycogenolysis.[4] Glucagon activates adenylate cyclase in the hepatic cell membrane to initiate glycogenolysis. Adenylate cyclase activation causes the formation of cyclic adenosine monophosphate, which acts via a second messenger system to precipitate a complex cascade of reactions leading to glycogenolysis.[4] Each succeeding product in the reaction is made in greater quantity than is the preceding product. Therefore, a small quantity of glucagon can produce large quantities of glucose.[4]

Glucagon also increases the rate of hepatic gluconeogenesis to maintain blood glucose even when hepatic glycogen stores are depleted. Glucagon activates required enzyme systems that normally serve as rate-limiting steps for gluconeogenesis. In addition, glucagon increases the extraction rate of amino acids from the bloodstream into hepatocytes, increasing available substrate for gluconeogenesis.[6]

Hepatic glycogenolysis and gluconeogenesis both result in the manufacture of glucose (Figures 1 and 2). Glucose is released into circulation from the liver and remains in circulation because a lack of insulin activity prevents cellular glucose uptake. Cellular glucose demand in the absence of insulin stimulates continued release of glucagon from pancreatic alpha cells, escalating hyperglycemia.[4] Hyperglycemia has a number of deleterious effects, including hyperosmolality and osmotic diuresis.[4,8,9] Hyperosmolality leads to dilutional hyponatremia from free water shifting from the interstitial space to the intravascular space. Osmotic diuresis exacerbates fluid loss and electrolyte wasting.[4]

To promote ketogenesis, glucagon acts on the hepatocyte (to cause a shift away from TG production in the hepatocellular cytoplasm) and to favor FFA formation and uptake by hepatic mitochondria in which ketogenesis occurs. Glucagon increases mitochondrial uptake of FFAs by decreasing hepatic malonyl coenzyme A concentration and increasing hepatic levels of carnitine.[1] Malonyl coenzyme A normally inhibits fatty acid oxidation to FFAs in the hepatic cytoplasm. With decreased levels of malonyl coenzyme A, FFA oxidation occurs to produce more substrate for ketogenesis. Esterification of FFAs with carnitine under the influence of the enzyme carnitine palmitoyltransferase I promotes entry into mitochondria.[1] Mitochondrial FFAs can enter the citric acid cycle for energy production or can be made into ketone bodies (i.e., acetoacetic and β-hydroxybutyric acid).[6] Because of the loss of insulin's inhibition of lipolysis at the hepatocyte, more FFAs are available for ketone formation. Lack of sufficient substrate for the citric acid cycle causes the mitochondria to become overwhelmed in their ability to convert FFAs to energy through the citric acid cycle.[6] As a result, ketoacid production soon exceeds the systemic ability to metabolize ketoacids, thus hyperketonemia occurs.[5] Ketoacids are released into the systemic circulation. Some acetoacetic acid will be converted to acetone, a volatile acid that is eliminated through the lungs. This acid causes ketone breath, which can be detected in some animals with DKA.[5,10] Because ketoacids are strong acids, once buffering systems become overwhelmed systemic acidemia results. When ketoacids are renally excreted with cations, they promote electrolyte wasting into the urine, exacerbating the osmotic diuresis caused by hyperglycemia (Figure 2).[11]

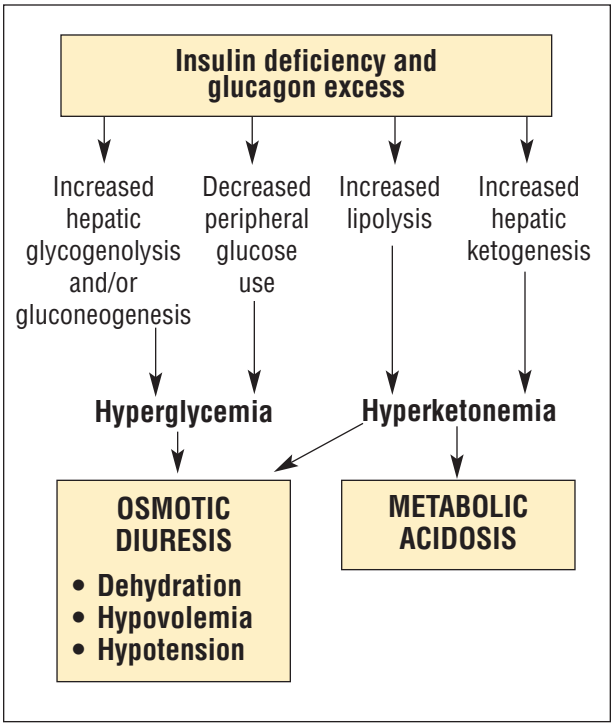

Figure 2—Schematic representation of the effects of a lack of insulin with concurrent hyperglucagonemia.

Stress Hormones

Other hormones that play a role in the pathogenesis of DKA include cortisol, epinephrine, and growth hormone. These hormones, collectively called *stress hor-*

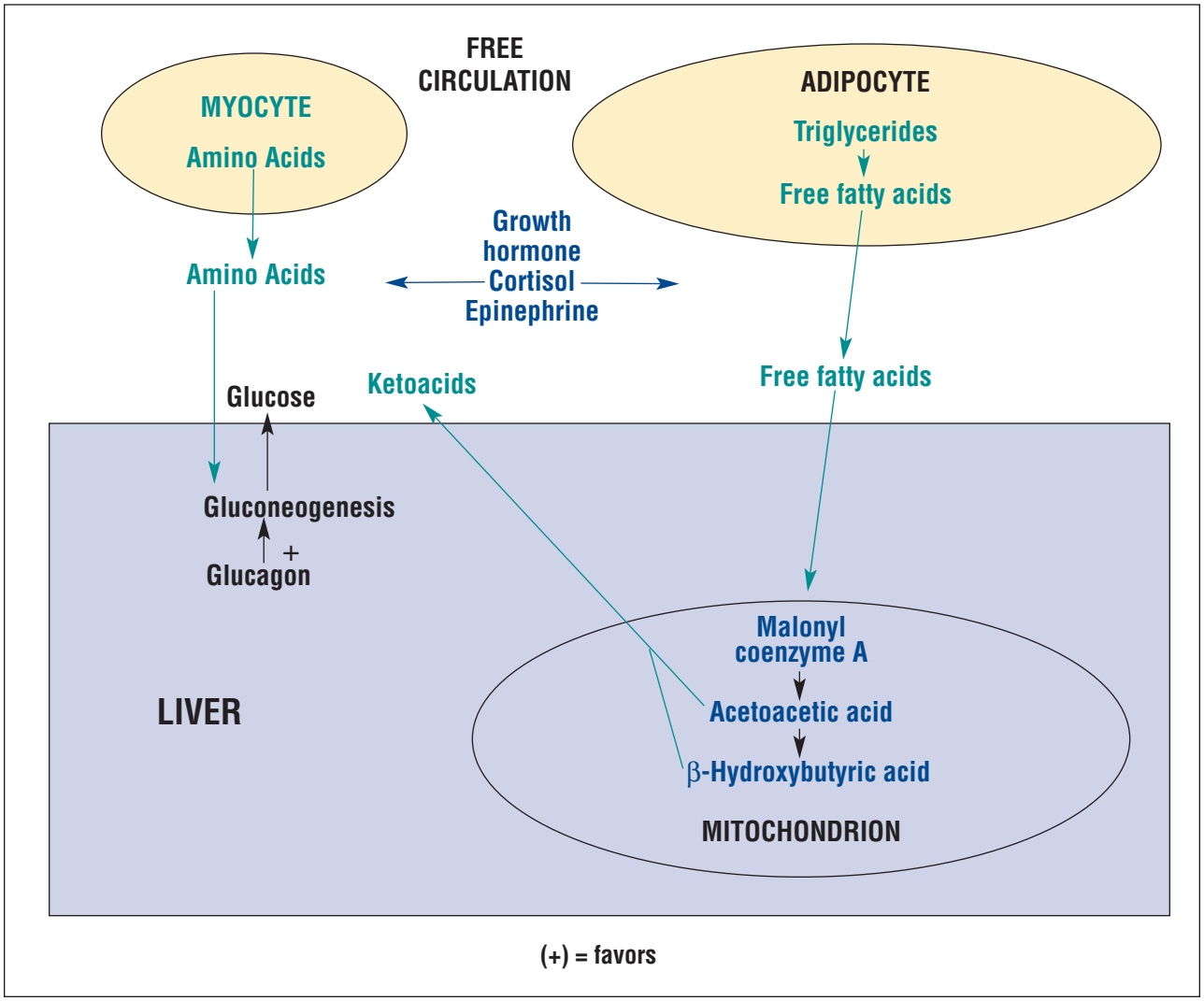

Figure 3—The stress hormones (i.e., cortisol, growth hormone, epinephrine) help facilitate available substrate via lipolysis of triglycerides to free fatty acids and muscle breakdown, causing the release of amino acids for hepatic gluconeogenesis by glucagon.

mones, perform a variety of activities that contribute to different aspects of DKA.[3,5] These chemical substances are lipolytic and elevate circulating FFA concentration in the absence of insulin.[7] These hormones promote insulin resistance through blockage of various cellular insulin receptors, thereby exacerbating hyperglycemia.[5] Cortisol and epinephrine act on the myocyte to promote muscle glycogenolysis and protein breakdown to release amino acids. Circulating amino acids provide substrate for hepatic gluconeogenesis to elevate blood glucose (Figure 3).[5,7]

CLINICAL PRESENTATION

Diabetic ketoacidosis causes critical illness resulting from dehydration, hyperosmolarity, electrolyte abnormalities, and acidemia.[10,12–14] Historically, the patient may have been previously diagnosed with DM or the client may have observed clinical signs of DM (e.g., polyuria; polydipsia; polyphagia; weight loss; dull, unkempt haircoat).[15] Uncommonly, dogs may present with rapid-onset blindness from diabetic cataracts, and cats may present with a plantigrade stance from peripheral neuropathy.[15] Despite the fact that insulin deficiency must precede DKA development, clients may not recognize signs of DM. Possible explanations include a short duration of lack of insulin activity; a recent, stressful event leading to decompensation; or difficulties observing an individual animal in a multiple-pet household.

The historical presentation of DKA in dogs and cats usually includes polyuria, polydipsia, weight loss, diminished activity, partial or complete anorexia, or vom-

Clinical Signs, Physical Examination Findings, and Serum Biochemical Changes Commonly Observed in Diabetic Ketoacidosis

Clinical and Historical Signs
- Anorexia
- Dehydration
- Lethargy
- Previous polyuria or polydipsia
- Vomiting or nausea
- Rapid-onset blindness (dogs)
- Plantigrade stance (cats)

Physical Examination Findings
- Dehydration
- Ketone breath
- Mental dullness
- Thin body condition
- Unkempt haircoat
- Weakness
- Cataracts (dogs)

Clinical Pathology Findings
- Azotemia
- Elevated hepatic transaminases
- Glucosuria
- Hypercholesterolemia
- Hyperglycemia
- Hypertriglyceridemia
- Hypochloremia
- Hypokalemia
- Hypomagnesemia
- Hyponatremia
- Hypophosphatemia
- Ketonuria
- Metabolic acidosis

iting.[10,12,13] Less frequently observed signs in cats include weakness, diarrhea, or gait change.[12,13]

Physical examination findings frequently include thin body condition, muscle wasting, lethargy, unkempt coat, dehydration, and hypothermia.[10,12,13] Hepatomegaly and icterus may be identified in some cats and dogs with DKA, but these findings seem to be less common in recent studies.[10,12,13,16,17] Other clinical signs in dogs include obesity, cataracts, and ketone breath.[10] Mild renomegaly or a plantigrade stance may be identified on physical examination of cats (see Clinical Signs, Physical Examination Findings, and Serum Biochemical Changes Commonly Observed in Diabetic Ketoacidosis).[12,15]

DIAGNOSTIC EVALUATION

In-Hospital Testing

Rapid confirmation of a diagnosis of DKA can often be accomplished in most veterinary hospitals. The four hallmarks of diagnosis are hyperglycemia, glucosuria, ketonuria, and metabolic acidosis, with appropriate clinical signs.[5]

Hyperglycemia can be rapidly identified using a portable blood glucose meter designed for capillary blood sampling for human diabetics, visual glucose color test strips, or point-of-care blood analyzer for veterinary blood testing.[18] The limitations of these methods include lack of specific correlation with serum biochemical analysis evaluation of glucose, whereas the advantages include rapid access to blood glucose determination and ease of use.[18,19] Variations in accuracy exist between brands of handheld monitors when used for veterinary applications; however, these devices can provide a blood glucose estimate during an emergency.[18] The results of visual glucose color test strips may be difficult to interpret depending on the tester's visual and color acuity.[18]

Glucosuria and ketonuria can be identified using a urine reagent strip that measures glucose and ketones. Glucosuria occurs when the blood glucose concentration is high enough that proximal renal tubular transport mechanisms, which remove glucose from the ultrafiltrate, become overwhelmed.[4] Diagnostic differentials for glucosuria include DM, stress hyperglycemia, intravenous dextrose infusion, and renal proximal tubular defect or damage.[20]

The ketone reagent on commercially available urine test strips uses a nitroprusside reaction that is activated by acetoacetic acid and acetone, not β-hydroxybutyric acid.[21,22] β-Hydroxybutyric acid production predominates in DKA patients; however, it would be extremely rare for patients to develop DKA with only an excess of β-hydroxybutyric acid.[5] In humans, when urine is unavailable, plasma ketones may be tested using a serum ketone test kit or by applying plasma to the reagent found in the urine test kit.[22] Correlation between urine and plasma ketone values using urine reagent strips is currently unknown for veterinary patients.

Metabolic acidosis is identified on the basis of low bicarbonate ion (HCO_3^-) and low pH on venous or arterial blood gas evaluation. When blood gas determination is not immediately available, treatment for DKA may be initiated based on hyperglycemia, glucosuria, ketonuria, and appropriate clinical signs.[5] Serum total carbon dioxide (TCO_2) should be below normal on the pretreatment serum sample when metabolic acidosis is present.[12,13] To further characterize metabolic acidosis caused by DKA, the calculated anion gap should be elevated. The anion gap represents the anions in circulation that are not measured routinely on serum biochemical analysis. Normal anion gap ranges from 12 to 20.[23] The anion gap is calculated by the following formula[23]:

$$\text{Anion gap} = [\text{Sodium (mEq/L)} + \text{Potassium (mEq/L)}] - [\text{Chloride (mEq/L)} + HCO_3^- \text{ (mEq/L)}]$$

An elevated anion gap indicates that unmeasured anions are present in the circulation after dissociation of an anion from an acid in circulation. In DKA, ketones become circulating unmeasured anions after dissociating from ketoacids. When significant dehydration is present, lactic acidosis from tissue hypoxia may contribute more unmeasured anions to further increase anion gap.[23]

Complete Medical Database

The medical database should include complete blood cell count, serum biochemical profile, urinalysis, and urine culture. Stress from a concurrent illness may precipitate an episode of DKA; therefore, additional testing should include radiography of the thorax and abdomen and ultrasonography of the abdomen. In cats, thyroxine level may be considered on an individual basis.[5] Dogs may have hyperadrenocorticism (HAC) concurrent with DKA; however, tests for HAC can show cortisol elevation when an animal is undergoing a stressful event.[24,25] Therefore, when HAC is suspected, clinicians should consider waiting until the DKA crisis has passed before conducting definitive HAC testing.

Complete blood cell count may show hemoconcentration when dehydration or, less commonly, anemia is present.[10,12,13] Neutrophilic leukocytosis is a common finding in cats.[12,13]

Serum biochemical analysis frequently shows elevated alanine aminotransferase, elevated aspartate aminotransferase, hypercholesterolemia, hypertriglyceridemia, high blood urea nitrogen (BUN), and high creatinine.[10,12,13,26] Hyperosmolarity is commonly identified as a result of hyperglycemia.[14] Electrolyte changes may include hyponatremia, hypochloremia, hypokalemia, hyperphosphatemia or hypophosphatemia, hypomagnesemia, and low total calcium.[10,12,13,26] Ionized calcium may be normal or low with low total calcium.[13] TCO_2 is frequently low because metabolic acidosis is a feature of DKA.[12,13]

Elevations of hepatic transaminases most likely occur secondary to dehydration, causing hypovolemia, poor hepatic oxygenation, and secondary hepatocellular damage.[27] Hypercholesterolemia and hypertriglyceridemia are caused by alterations in lipid metabolism in the absence of insulin.[28] High BUN and creatinine may represent prerenal azotemia or renal azotemia from preexisting renal disease.[5]

Hyperosmolality is usually present in DKA.[12,13] Osmotic force is determined by the number of particles in solution. Fluid will move across a semipermeable membrane from an area of lesser particle concentration to an area of greater concentration. Serum osmolality may be approximated by the following formula[23]:

Calculated osmolality = 2[Sodium (mEq/L) + Potassium (mEq/L)] + BUN (mg/dl)/2.8 + Glucose (mg/dl)/18

Sodium and potassium are doubled to account for their corresponding anions. Glucose and BUN are divided by a factor because their large particle size reduces the particle number in each unit of measure. BUN does contribute to osmolality; however, it does not significantly contribute to fluid shifting because it will equilibrate across semipermeable membranes easily.[23] Significant hyperglycemia must be present to affect osmolality.

Generation of hyperosmolarity from hyperglycemia is instrumental in causing hyponatremia and hypochloremia associated with DKA. As osmolality increases, free water shifts from the interstitial to the intravascular space, and intravascular sodium and chloride concentrations decrease by dilution. This dilution should occur in a predictable manner based on blood glucose elevation; therefore, the following formula could be used to correct sodium[3]:

Corrected sodium = Sodium + {1.6 x [Glucose (mg/dl) – 100]/100}

For example, if the patient's glucose level is 700 mg/dl and measured sodium is 131 mEq/L, corrected sodium would be 140.6 mEq/L. If the corrected sodium is in the normal range, hyponatremia is caused by free water shifting from the interstitial to the intravascular space because of hyperglycemia, and measured sodium should correct with reduction of blood glucose. If the corrected sodium is still below normal, sodium wasting has also occurred from chronic osmotic diuresis.

With DKA, measured sodium is often in the normal range even with significant hyperglycemia.[10,12] Normal serum sodium levels in these patients are inappropriate and represent excess free water loss, most likely secondary to failure to replace ongoing urinary fluid losses by drinking. Significant hyperosmolarity exists in these patients, both from hypernatremia as well as from hyperglycemia.

With excessively rapid correction of hyperosmolarity from rapid glucose reduction or excessive free water administration, cerebral edema and neurologic dysfunction may result. Various proposed mechanisms may cause cerebral edema formation: (1) when DKA is untreated, osmotically active particles may form within the brain parenchyma and cause fluid to shift into the brain, and (2) when blood glucose falls rapidly following insulin therapy, alterations of the blood–brain barrier may occur.[5]

Hypokalemia is the most common electrolyte abnor-

mality detected in patients with DKA.[10,12,28–30] Potassium is the major intracellular cation, and serum potassium does not adequately reflect total body potassium content.[23] DKA predisposes patients to total body potassium depletion by various mechanisms. First, chronic metabolic acidosis from ketoacidosis causes potassium to shift to the extracellular space. Second, osmotic diuresis from hyperglycemia and glucosuria promotes increased renal loss of potassium. Finally, with vomiting and anorexia, potassium is lost through the gastrointestinal tract and not replaced.[30] Hypokalemia may be mild or may not be evident on initial testing. Potassium levels may drop precipitously with institution of therapy that includes potassium-poor fluids, resolution of metabolic acidosis, and insulin therapy, causing intracellular shifting of potassium.[23,30]

Hyperphosphatemia may be present with dehydration or preexisting renal disease from reduced glomerular filtration. Hyperphosphatemia usually causes low total calcium, thus enabling the calcium phosphate solubility product to remain constant.[31]

Hypophosphatemia may be seen initially or with treatment of DKA. Phosphorus is the major intracellular anion.[31] It is important for energy production (in ATP formation and as a cofactor for glycolysis) and for cell membrane maintenance (needed to form 2,3-diphosphoglycerate and used as a component of phospholipid membrane).[32] Phosphorus is regulated by dietary intake, renal excretion, factors that promote ion movement into and out of cells (e.g., insulin, glucose, blood pH), and vitamin D and parathyroid hormone interactions.[31,32]

Although hypophosphatemia is an uncommon finding on initial serum biochemical profile of patients with DKA, it may be anticipated following intravenous fluid and insulin therapy.[12,13] Following insulin administration in patients with chronic phosphorus wasting, glucose and phosphorus will shift suddenly intracellularly, causing or exacerbating hypophosphatemia. When phosphorus levels decrease below 1 mg/dl, clinical signs of hypophosphatemia may occur. Acute hemolytic anemia may occur from lack of 2,3-diphosphoglycerate production, causing erythrocyte energy loss and membrane rupture.[32–35] Other signs of hypophosphatemia include lethargy, depression, and diarrhea.[34]

Magnesium deficiency and hypomagnesemia may occur with poor oral intake, increased renal loss, or changes in distribution.[34] In humans with DM and DKA, a 30% to 55% incidence of hypomagnesemia has been reported.[36] Clinical manifestations of hypomagnesemia include neuromuscular weakness, cardiac arrhythmia, hypokalemia, and hypocalcemia.[37] Many humans with hypomagnesemia remain asymptomatic, and the onset of symptoms may be dictated more by the rate of decline than by the absolute number.[37] Traditionally, serum total magnesium levels have been used to diagnose magnesium deficiency. However, serum total magnesium can be within normal limits when total body hypomagnesemia exists because serum contains less than 1% of total body magnesium.[38] Alternatively, ionized magnesium concentrations may provide a more accurate assessment of total body magnesium stores because serum ionized magnesium should more closely equilibrate with extracellular ionized magnesium.[39] In normal cats fed a magnesium-deficient diet, serum total and ionized magnesium concentrations were closely correlated.[40] In a recent study of magnesium concentrations in cats with DM and DKA, ionized magnesium levels were more commonly below normal limits when compared with serum total magnesium levels at the time of admission, whereas serum total magnesium levels that were normal at admission significantly decreased when cats received intravenous fluid treatment over a 48-hour period.[36] Serum total magnesium assessment is more commonly available than is ionized magnesium through most commercial laboratories. In situations in which only serum total magnesium is available, serial magnesium measurements, or measurement 1 to 2 days after initiation of therapy, may assist in diagnosis of hypomagnesemia in DKA patients.[36]

Low serum TCO_2 or plasma HCO_3^- frequently occurs with DKA and is indicative of metabolic acidosis caused by ketoacid production and lactic acid production with cellular dehydration.[10,12,13,41] Ketonemia results in metabolic acidosis with an increased anion gap and ketonuria.[41]

Concurrent illnesses that have been identified in dogs with DM or DKA include urinary tract infection, pancreatitis, HAC, or renal impairment.[10,29] Concurrent illnesses that have been identified with DM or DKA in cats include hyperthyroidism, inflammatory bowel disease, eosinophilic granuloma complex, hepatic lipidosis, cholangiohepatitis, chronic renal disease, or pancreatitis.[12,13] Previous administration of corticosteroids or megesterol acetate may be identified in some patients.[10,12,13] Concurrent illnesses or corticosteroid therapy may increase the complexity of diagnostic testing and treatment of DKA.[28]

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ARTICLE #1 CE TEST

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1. The initiating event for DM, and subsequently DKA, is
   a. an increased level of circulating stress hormones.
   b. loss of pancreatic alpha cell function to produce insulin.
   c. lack of insulin activity from poor production or receptor failure.
   d. loss of pancreatic beta cell function to produce glucagon.
   e. glucosuria, causing osmotic diuresis and loss of insulin.

2. Activities of glucagon include
   a. maintenance of blood glucose by suppression of hepatic glycogenolysis.
   b. maintenance of blood glucose by suppression of peripheral ketone use.
   c. maintenance of blood glucose by promoting gluconeogenesis.
   d. promoting ketogenesis by increasing malonyl coenzyme A.
   e. promoting ketogenesis by suppressing hepatic carnitine levels.

3. Stress hormones
   a. include cortisol, growth hormones, and insulin.
   b. increase insulin resistance in peripheral tissues.
   c. inhibit amino acid release from myocytes.
   d. increase ketone production by increasing malonyl coenzyme A.
   e. decrease FFA release from adipocytes.

4. Insulin activities include promotion of
   a. lipolysis.
   b. cellular glucose uptake.
   c. ketogenesis.
   d. hyperglycemia.
   e. amino acid breakdown.

5. Which of the following historical presentations occurs frequently with DKA but not DM?
   a. polydipsia
   b. weight loss
   c. polyuria
   d. polyphagia
   e. vomiting

6. Hallmarks of diagnosing DKA include all of the following except
   a. decreased anion gap.
   b. hyperglycemia.
   c. ketonuria.
   d. glucosuria.
   e. appropriate clinical signs.

7. Anion gap
   a. is created by excess blood glucose.
   b. implies an excess of circulating anions to cations.
   c. is usually decreased in DKA.
   d. is increased by circulating ketone bodies.
   e. will increase with appropriate therapy.

8. A complete medical database for DKA should include all of the following except
   a. complete blood cell count.
   b. urinalysis.
   c. corticotropin hormone stimulation test.
   d. urine culture and sensitivity.
   e. serum biochemical profile.

9. Osmotic force
   a. is determined by the unmeasured anions in circulation.
   b. dictates fluid movement from an area of greater to lesser concentration of particles.
   c. is most strongly influenced by BUN concentration.
   d. is increased with significant hyperglycemia.
   e. dictates fluid movement across an impermeable membrane.

10. Dogs and cats with DKA
    a. may have other illnesses that complicate therapy.
    b. rarely present with polyuria and polydipsia.
    c. are commonly observed to be polyphagic.
    d. are commonly found to be hypertensive.
    e. have no differences in clinical presentation.