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Abstract

Hyperglycemic hyperosmolar syndrome (HHS) is a serious complication of diabetes mellitus. It resembles another complication of diabetes mellitus, diabetic ketoacidosis, in that both involve hyperglycemia; however, HHS patients experience more severe hyperglycemia without ketoacidosis. Knowing the difference and promptly and correctly treating HHS are key. Treatment involves stabilizing fluid volume, sodium, and glucose; administering insulin; and supplementing electrolytes. Patient mortality rates can be high and nursing care intensive.

CONTINUING EDUCATION

ENDOCRINOLOGY

Diabetes: Hyperglycemic Hyperosmolar Syndrome

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Diabetes mellitus (DM) and diabetic ketoacidosis (DKA) are common endocrine disorders of the pancreas, seen in general practice and emergency/critical care settings. Lesser known, and even less understood, is a serious complication of diabetes mellitus: hyperglycemic hyperosmolar syndrome (HHS), also called hyperosmolar hyperglycemic state. HHS and DKA are similar in some respects, but differentiating between them is crucial for effective treatment. This article covers what HHS is, what makes HHS rather than DKA develop in a diabetic patient, and how to treat and care for patients with HHS. Awareness of this syndrome and its clinical signs enables veterinary nurses to aid with diagnosis and proper care and treatment of the HHS patient.

WHAT IS HHS?

HHS is a serious complication of DM that develops when blood glucose levels are too high for a long time, leading to severe dehydration and confusion. HHS is one extreme of decompensated, uncontrolled DM; the other extreme is DKA (**TABLE 1**). Both DKA and HHS represent serious complications of DM and result in increased illness and death.

HHS has long been considered to be rare among diabetic patients. One retrospective study detected this syndrome in only 5% of dogs with DM.[1] However, the concept of HHS being rare can be challenged by considering that HHS is often overlooked and treated/diagnosed as DKA and by accepting that DKA and HHS can often overlap.

Take-Home Points

- For proper treatment, hyperglycemic hyperosmolar syndrome (HHS) must be distinguished from diabetic ketoacidosis (DKA).
- Clinical signs of HHS include dehydration, hypothermia, lethargy, depression, and possibly even coma.
- Typical laboratory findings are severe hyperglycemia, hyperosmolality, glucosuria, trace or absent ketones, and mild to no metabolic acidosis.
- Treatment involves slowly stabilizing fluid, sodium, and glucose levels; administering insulin; and supplementing electrolytes.
- Treatment and nursing care of HHS patients can be far more intensive and complicated than that of DKA patients.

Hence, familiarity with the diagnostic criteria of HHS is crucial for veterinary nurses as treatment of HHS is more intensive and slower than that of DKA, and clients must be aware of the potential risks, prognosis, and costs involved with treatment.

HOW DOES HHS DEVELOP?

Most (69% to 92%) patients with DKA or HHS have a concomitant infection or disease,[2] which may affect, and worsen, the patient's clinical status. In humans, infection preceding onset of HHS has been well documented.[3] Additional precipitating factors include cerebrovascular accident, mesenteric ischemia, acute pancreatitis, or medications (e.g., steroids, thiazide diuretics, calcium channel blockers, propranolol). In veterinary patients, events leading up to manifestations of this syndrome often include gastrointestinal abnormalities, neurologic issues such as weakness that may be progressive, anorexia, vomiting, and lethargy. Patients with HHS may have a previous or new diagnosis of DM. Patients with HHS or DKA have either a relative (HHS) or absolute (DKA) deficiency of insulin,[3] possibly with an overabundance of counter-regulatory hormones (glucagon, adrenaline, cortisol, growth hormone).

Insulin is produced from β-cells in the islets of Langerhans, located in the pancreas. In patients with DM, DKA, or HHS, these cells are not producing enough, or any, insulin. Insulin deficiency results in elevated levels of glucagon, catecholamines, and cortisol, which all serve to promote glycogenolysis and gluconeogenesis in the liver. Elevated levels of cortisol (hypercortisolemia) promote proteolysis, which provides the amino acid precursors needed for gluconeogenesis.

When the liver is stimulated to produce glucose, cells are unable to use it due to lack of insulin and high concentrations of catecholamines, which also reduce uptake of glucose by peripheral tissues. The combination of increased production of glucose and decreased use or uptake of glucose results in hyperglycemia, which leads to glucosuria, which causes an osmotic diuresis, increased fluid loss, and subsequent dehydration. In the HHS patient, dehydration will also lead to decreased kidney perfusion, which results in less glucose excretion and worsening hyperglycemia.

It is believed that diabetic patients with HHS have some functioning β-cells and thus some circulating plasma insulin.[3-5]

WHY DOES HHS DEVELOP INSTEAD OF DKA IN SOME PATIENTS?

In the DKA patient, the combination of absolute insulin deficiency and elevated catecholamines, cortisol, and growth hormones activates the release of hormone-sensitive lipase. Lipase aids in breaking down triglycerides and releases free fatty acids from adipose tissue (lipolysis). These fatty acids are taken up by the liver to be oxidized; however, without insulin, ketone bodies are produced instead (ketogenesis). Accumulation of ketone bodies results in the classic DKA triad of hyperglycemia, hyperketonemia, and acidemia, which is accompanied by osmotic diuresis, with glucosuria and ketonuria.

In the HHS patient, ketogenesis does not occur. It is believed that diabetic patients with HHS have some functioning β-cells and thus some circulating plasma insulin.[3-5] The insulin deficiency in HHS patients is relative. The small amounts of insulin prevent development of ketosis by preventing lipolysis. Because lipolysis does not occur at the same rate, availability of precursor free fatty acids is limited, which in turn restricts the rate of ketone formation. Patients with HHS may also have hepatic resistance to glucagon, which would also result in the lack of ketosis.

HHS patients thus start with a relative lack of insulin and persistent hyperglycemia, which leads to osmotic diuresis and counter-regulatory hormone release. The small amount of insulin prevents hyperketonemia; however, osmotic diuresis drives loss of water and sodium, and hyperglycemia itself causes movement of water from the interstitial and intracellular spaces to intravascular spaces, further diluting the sodium. The osmotic diuresis, along with vomiting and decreased water intake, compounds the severity of dehydration. Hyperglycemia becomes increasingly severe due to substantial dehydration, reduced glomerular filtration rate (GFR), and decreased excretion of glucose in urine.

FIGURE 1. A dog with hyperglycemic hyperosmolar syndrome, exhibiting central nervous system depression and obtundation.

BOX 1

Criteria for Hyperglycemic Hyperosmolar Syndrome Diagnosis

- Glucose >600 mg/dL
- Serum osmolality >320 mmol/L
- Profound dehydration (>8%)
- pH >7.3
- Bicarbonates >15 mEq/L
- Low-level ketonuria
- Absent to low ketonemia
- Altered level of consciousness

GFR is reduced due to dehydration, hypovolemia, and concomitant diseases (e.g., chronic kidney or heart failure/disease, shock). Lack of ketosis in HHS patients removes the recognizable clinical signs of metabolic acidosis; therefore, hyperglycemia in the HHS patient often persists substantially longer, until the signs of severe hyperosmolality begin.

Severe hyperosmolality causes dehydration of neurons in the brain, which can result in various neurologic signs, with severity depending on how quickly and how severe the osmolality changed. Neurologic signs typically appear when plasma osmolality is >340 mmol/L, which is when fluid shifts from intracellular to extracellular space to maintain equilibrium. To protect the brain, the body responds by forming idiogenic osmoles (organic particles that can accumulate in high concentrations without adversely affecting cell structure or function), which help maintain cerebral fluid balance.

HOW IS HHS DIAGNOSED?

Clinical Signs

Initial examination of the HHS patient will reveal profound dehydration, hypothermia, lethargy, extreme depression, and, less commonly, coma (**FIGURE 1**, **BOX 1**). Abdominal pain and vomiting are common. Hyperosmolality may lead to the neurologic signs of altered level of consciousness, abnormal pupillary light reflexes, circling, pacing, and seizures. Signs of concomitant disease, especially heart disease, may be noted. Heart murmur, arrhythmias, increased respiratory rates, prolonged capillary refill time, and low blood pressure may all be found. In patients with

TABLE 1 Relative Characteristics of HHS Versus DKA

CHARACTERISTIC	HHS	DKA
An extreme of decompensated, uncontrolled DM	Yes	Yes
Hyperglycemia	Yes (>600 mg/dL)	Yes
Hyperosmolality	Yes (>320 mmol/L)	No (+/– Yes)
Ketoacidosis	No	Yes
Intensity of care requirements	More	Possibly less
Recommended fluid replacement rate	Slower	Not as slow
Electrolyte supplementation	Same	Same
Mortality rate	Higher	Moderate
Outcome if treated as DKA	Poor	Guarded

DKA = diabetic ketoacidosis; DM = diabetes mellitus; HHS = hyperglycemic hyperosmolar syndrome

BOX 2

Calculations

Corrected sodium: Measured sodium + [(serum glucose – 100) × 1.6[a]]

Plasma osmolality[b]: 2(Na+K) + glucose/18 + blood urea nitrogen/2.8

[a]×2.4 if glucose >400 mg/dL
[b]To accurately calculate plasma osmolality, if glucose levels are above range of an analyzer, samples must be diluted to achieve an endpoint number.

chronic kidney disease, clinical signs of uremia may be noted, including oral ulcerations and halitosis.

Laboratory Findings

Typical laboratory findings for patients with HHS include severe hyperglycemia (>600 mg/dL or >33.3 mmol/L),[3] hyperosmolality (>320 mmol/L),[5] glucosuria, trace or absent ketones, and mild to no metabolic acidosis (pH >7.3) (**TABLE 1**). In addition, packed cell volume (PCV) may be elevated due to dehydration. If the patient also has chronic kidney disease, the PCV may initially seem normal but later reveal anemia after fluid resuscitation due to anemia of chronic disease. Azotemia (prerenal or renal) and hyperphosphatemia may also be present. Electrolyte abnormalities are common, although they may not be fully revealed until treatment is initiated. Hyperglycemia causes water and potassium to shift from intracellular to extracellular fluid spaces. In addition, excessive amounts of potassium are lost through osmotic diuresis and vomiting. In HHS patients, potassium depletion may be profound, although testing may initially show a normal or even elevated potassium level. Sodium can be falsely decreased due to hyperglycemia, and corrected sodium levels should be calculated (**BOX 2**), after which the patient may be found to be normonatremic or even hypernatremic, rather than hyponatremic. Additional amounts of chloride may also be lost through the same mechanisms as potassium and sodium, resulting in hypochloridemia. Magnesium, phosphorus, and calcium should also be monitored in these patients and supplemented accordingly.

Because HHS can overlap with DKA, plasma osmolality should be calculated (**BOX 2**), especially for patients with neurologic signs and for all hospitalized patients with DM. Osmotically active particles such as sodium, glucose, and blood urea nitrogen (BUN) influence water shifting through semipermeable membranes. BUN is not always included in the calculation of effective osmolality because it is freely permeable in and out of the intracellular compartment; however, it may be included in the formula when severe azotemia is present, which is common for HHS patients. Normal plasma osmolality is approximately 290 mmol/L. A patient is considered hyperosmolar when plasma osmolality is >310 mmol/L, but osmolality must be >320 mmol/L (some sources say >350 mmol/L) for a diagnosis of HHS.

WHAT ARE THE TREATMENT AND CARE FOR AN HHS PATIENT?

Treatment

Fluid Resuscitation

Circulating fluid volume in HHS patients is often depleted, requiring rapid restoration to ensure a positive outcome. However, to adequately restore volume without lowering plasma osmolality too quickly requires careful monitoring. Treatment includes careful fluid therapy, calculating the patient's dehydration deficit, and replacing 80% of this deficit over 36 to 48 hours.[5] This rate is much slower than that

TABLE 2 Sodium Content in Fluids

FLUID	SODIUM, mEq/L
0.9% sodium chloride solution	154
Ringer's lactate solution	130
Plasma-Lyte/Normosol-R	140
0.45% sodium chloride solution	77
5% dextrose in water	0

recommended for the typical DKA patient. Fluid therapy should also replace ongoing losses in addition to dehydration deficits and daily maintenance.

Initially, fluid resuscitation is needed to correct large volume deficits. Idiogenic osmoles cannot dissipate rapidly; therefore, rapid reduction of plasma osmolality could create a gradient and shift water into the neurons, causing cerebral edema. Thus, when IV fluid is administered, caution must be taken to not lower the plasma osmolality too quickly and cause cerebral edema and worsen neurologic signs. Osmolality must be decreased very slowly, at a rate of no more than 10 to 15 mOsm/day, while monitoring changes in sodium and glucose and recalculating osmolality every 2 hours.

When IV fluid is administered, caution must be taken to not lower the plasma osmolality too quickly and cause cerebral edema and worsen neurologic signs.

Sodium

Sodium levels should be decreased slowly; if high (using corrected sodium) over a minimum of 72 hours, decrease at a rate of 0.5 to 1 mEq/h (10 to 12 mEq/day). Always give a balanced isotonic fluid with a sodium content closest to the patient's current plasma-corrected sodium level. Often, the best initial choice for an HHS patient, given for a minimum of 4 to 6 hours, is generally considered to be 0.9% sodium chloride (if cardiac disease is not present and if the sodium concentration is closest to the patient's current correct sodium).[3-5]

Glucose

IV fluid administration will restore the extracellular fluid volume and stimulate an increase in GFR, both of which will aid in reducing glucose levels by 30% to 50%.[2] Glucose levels must be lowered more slowly for HHS patients than for DKA patients, at a rate of only 50 to 75 mg/dL/h. Because sodium is also in the fluid, the fluid type must be carefully chosen (**TABLE 2**). As glucose concentration is lowered, less fluid is shifted, which will help normalize sodium levels if they were initially low. Electrolytes, including sodium and potassium, should be rechecked frequently (every 4 hours initially) and fluids adjusted accordingly.

FIGURE 2. Multilumen central line in dog with hyperglycemic hyperosmolar syndrome.

Insulin

Therapy with regular insulin delivered as a constant rate infusion (CRI) may begin 4 to 6 hours after fluid therapy has begun or when the patient has been stabilized. Some sources recommend that insulin dosage for HHS patients (1 U/kg for dogs and 0.5 U/kg for cats)[3] be lower than the standard dosage for DKA patients, which makes sense as glucose levels must be lowered more slowly for HHS patients than for DKA patients. Monitoring must be diligent to ensure that glucose levels are lowered no faster than at a rate of 50 to 75 mg/dL/h (2.77 to 4.16 mmol/L),[5] which will also help lower plasma osmolality slowly over the course of treatment. Other sources cite standard insulin CRI dosages as used for DKA patients. As long as glucose levels are decreased slowly enough, in a controlled manner, either regimen has merit.

Electrolytes

Electrolytes should be supplemented as needed. Supplementation for HHS patients is typically similar to that needed by DKA patients. However, for patients with acute kidney injury or chronic kidney disease, care should be taken with regard to supplementing potassium and phosphorus. Electrolytes should be monitored much more frequently for HHS patients (every 1 to 2 hours initially, then every 4 to 6 hours) than for standard DKA patients due to the

complications posed by acute kidney injury and chronic kidney disease.[6] Do not forget to check magnesium levels in these patients, as these electrolytes can deplete rapidly, are often overlooked, and can have life-threatening results.

Nursing Care

Central lines in HHS patient are useful because of the frequent need for blood sampling, glucose testing (eevry 1 to 2 hours), electrolyte testing (every 4 to 6 hours), and blood chemistries (every 24 hours) (**FIGURE 2**). Development of subclinical cerebral edema within the first 24 hours is not uncommon.[6] The degree of mental obtundation in HHS patients can require extensive nursing care (e.g., scheduled rotation of body position, passive range of motion therapy, maintaining patient cleanliness, lubricating eyes).

Consider placing a urinary catheter in HHS patients, especially those with azotemia. Catheters enable close monitoring of total urinary losses to ensure that the patient is producing adequate amounts of urine (minimum 1 to 2 mL/kg/h if receiving IV fluids) and to account for polyuria resulting from osmotic diuresis. Urinary catheters also help keep HHS patients clean as these patients are often recumbent, at least initially.

Frequent monitoring of all vital signs (temperature, heart rate, respiratory rate, mucous membranes, capillary refill time, hydration status) for HHS patients is key, starting hourly for some patients and never longer than every 4 hours. HHS patients are often hypothermic and need external heat support with frequent temperature monitoring. Checking the patient's body weight every 6 to 12 hours throughout hospitalization is helpful for guiding fluid therapy.

PROGNOSIS

The mortality rate is higher for HHS than for DKA patients; for humans, mortality rates vary from 15% to 17%.[3] Because acute kidney injury/chronic kidney disease is common among veterinary patients, the overall long-term survival rate for these patients is very low. One study found that 65% of cats with HHS did not survive to discharge; long-term survival rate was 12%.[7] A retrospective study of 66 dogs found that 62% survived to discharge.[1]

SUMMARY

HHS represents one of the more challenging complications of DM. Quick recognition of the clinical signs and diagnostic criteria is vital for the patient's outcome. HHS and DKA can overlap in the same patient; however, true HHS occurs more frequently than recognized. If HHS is improperly treated as typical DKA, the outcome will likely be poor. Nursing care for the HHS patient is intensive, and although it carries a poor prognosis overall, when patients do survive, the work can be very rewarding. TVN

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Angela obtained her CVT certification in 1990. She began working in emergency and critical care medicine in 1995 and obtained her VTS certification in emergency and critical care in 2001. She has been a charter member of the Academy of Veterinary Internal Medicine Technicians since 2008, past president of a previous state technician association in Arizona, and has served as the chair for the examination committee and executive secretary of the Academy of Veterinary Emergency & Critical Care Technicians and Nurses for 7 years. Angela received awards for Arizona Veterinary Medical Association Technician of the Year in 2001 and Viticus/WVC Continuing Educator of the Year in 2022. She has lectured internationally for over 20 years and published many articles. She currently works as an advanced practice veterinary nurse for the Veterinary Emergency Group in Dallas, Texas.

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CONTINUING EDUCATION

Diabetes: Hyperglycemic Hyperosmolar Syndrome

TOPIC OVERVIEW

Hyperglycemic hyperosmolar syndrome (HHS) and diabetic ketoacidosis (DKA) are serious complications of diabetes mellitus that resemble each other in some respects. It is essential to differentiate them before proper nursing care and treatment can be initiated, as HHS can be far more intensive and complicated to treat than DKA.

LEARNING OBJECTIVES

Readers will be able to distinguish the clinical signs of hyperglycemic hyperosmolar syndrome from those of diabetic ketoacidosis, recall the differing etiologies and prognoses for these conditions, and demonstrate the appropriate treatment and nursing care protocols for patients with HHS.

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1. **Serum osmolality (mmol/L) in hyperglycemic hyperosmolar syndrome (HHS) patients is which of the following?**
   a. <290
   b. 290 to 300
   c. 300 to 310
   d. >320

2. **Which of the following is never included in the calculation for plasma osmolality?**
   a. Sodium
   b. Potassium
   c. Creatinine
   d. Blood urea nitrogen

3. **Both osmolality and sodium levels must be lowered very slowly in the HHS patient. What are the maximum rates that each can be lowered, respectively?**
   a. 10 to 12 mOsm/day and 10 to 15 mEq/day
   b. 10 to 15 mOsm/day and 10 to 12 mEq/day
   c. 15 to 20 each (mOsm/day and mEq/day)
   d. No more than 10 each (mOsm/day and mEq/day)

4. **The goal is to lower the blood glucose how quickly in the HHS patient?**
   a. 25 to 50 mg/dL/h
   b. 50 to 75 mg/dL/h
   c. 50 to 100 mg/dL/h
   d. 75 to 100 mg/dL/h

5. **Which of the following is a typical pH for an HHS patient?**
   a. <7.2
   b. <7.1
   c. >7.3
   d. >7.5

6. **Which of the following is the most common amount of ketones in the urine of an HHS patient?**
   a. Large
   b. Moderate
   c. Small
   d. None

7. **All of the following laboratory abnormalities are commonly found in HHS patients EXCEPT:**
   a. Anemia
   b. Azotemia
   c. Hypernatremia
   d. Hyperkalemia

8. **What is the minimum acceptable urine production of a patient on IV fluids?**
   a. 0.5 to 1 mL/kg/h
   b. 1 to 2 mL/kg/h
   c. 2 to 3 mL/kg/h
   d. Same as rate of fluid administration

9. **True or false: Survival rate for HHS patients is the same as that for diabetic ketoacidosis patients.**
   a. True
   b. False

10. **For the HHS patient, 80% of the dehydration deficit should be replaced over how many hours?**
    a. 12
    b. 12 to 24
    c. 24 to 36
    d. 36 to 48