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Abstract

Objectives – To clinically characterize a large group of dogs with the hyperosmolar hyperglycemic state (HHS) and to determine whether 2 HHS subgroups, dogs with hyperosmolar ketonuric (HK) diabetes mellitus (DM) and dogs with hyperosmolar nonketonuric (HNK) DM were clinically different from one another.

Design – Retrospective study. Records of 1,250 diabetic dogs that were examined between January 1993 and July 2008 were reviewed in order to identify dogs with HHS. Inclusion required a calculated serum osmolality ≥325 mOsm/kg, with or without ketonuria.

Setting – University teaching hospital.

Animals – Sixty-six dogs with HHS including 34 dogs with HK, 25 dogs with HNK, and 7 dogs with unclassified HHS.

Interventions – None.

Measurements and Main Results – HHS was diagnosed in 5% of dogs with DM. HK and HNK dogs were similar to one another in regard to most historical, physical examination, and clinicopathologic variables as well as outcome. Sixty-two percent of dogs with HHS survived to discharge from the hospital. Poor outcome of HHS dogs was associated with abnormal mental status (P = 0.03) and a low venous pH (P = 0.045). Dogs with HK were significantly more likely to have acute pancreatitis (P = 0.046), higher body temperature (P = 0.006), higher WBC count (P = 0.01), and a shorter duration of clinical signs (P = 0.02) compared to dogs with HNK. Dogs with HNK had significantly higher BUN and creatinine concentrations (P = 0.0002 and P = 0.008, respectively) and higher calculated osmolality (P = 0.001) compared to dogs with HK.

Conclusions – HHS is a rare condition in which poor outcome is associated with abnormal mental status and low venous pH. Among dogs with HHS, the subgroup of dogs with HK has significantly more acute pancreatitis, shorter duration of clinical signs, and higher body temperature and WBC count compared to dogs with HNK, whereas dogs with HNK have more azotemia and higher calculated osmolality compared to dogs with HK.

Keywords: acid-base status, canine, diabetes mellitus, nonketotic, ketosis

Introduction

The hyperosmolar hyperglycemic state (HHS) is a diabetic complication characterized by severe serum hyperosmolality. In recent years, this state has evolved to include hyperosmolar human diabetics with or without excess ketone concentrations. Historically, diabetic ketoacidosis (DKA) was considered a distinctly separate entity from hyperosmolar nonketonuric (HNK) diabetes mellitus (DM). However, more recently, it has become apparent that features of DKA and HNK can develop

Abbreviations

BCS  body condition score  
DM  diabetes mellitus  
HHS  hyperosmolar hyperglycemic state  
HK  hyperosmolar ketonuric DM  
HNK  hyperosmolar non-ketonuric DM  
UTI  urinary tract infection  
DKA  diabetic ketoacidosis  
ADA  American Diabetes Association

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The authors declare no conflict of interests.

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simultaneously, and 30% of human patients examined for a diabetic emergency have a mixed state of DKA and HNK diabetes characterized by both ketoacidosis and hyperosmolarity. The American Diabetes Association (ADA) has therefore recommended using the term HHS to include patients with HNK as well as those with hyperosmolar ketonuria (HK). 1-2

In dogs, HHS has not yet been described, although HNK is infrequently reported. 3-6 Original reports of hyperosmolality in diabetic dogs are rare, and current accepted knowledge is based largely on case reports, textbook chapters, or conference proceedings. 3-5 The largest original study of osmolality in diabetic dogs, reported thus far in the literature, defined hyperosmolality as an osmolality > 310 mOsm/kg, and marked hyperosmolality as > 330 mOsm/kg. 6 This study of 14 diabetic dogs identified severe hyperosmolality (> 330 mOsm/kg) in 3 dogs. 9 The present study chose a serum osmolality ≥ 325 mOsm/kg as the cutoff for hyperosmolality in diabetic dogs in an attempt to include a relatively large range of diabetic dogs that definitively had hyperosmolality.

The first goal of this study was to characterize the HHS in a large group of dogs and provide a comprehensive description of the signalment, clinical signs, physical examination, clinopathologic, and imaging findings, as well as outcome of dogs with HHS. The second goal was to determine if 2 subgroups of dogs with HHS, dogs with HK and dogs with HNK, were clinically different from one another. It was hypothesized that among dogs with a calculated serum osmolality ≥ 325 mOsm/kg, the 2 subgroups of dogs with HK and HNK would be clinically similar to one another.

Materials and Methods

Criteria for selection of cases

A computer search for a coded diagnosis of DM in all dogs examined at a university veterinary teaching hospital between January 1993 and July 2008 identified 1,250 dogs with DM. Medical records were reviewed in detail by a board-certified internal medicine specialist. Upon review of the medical records, 66 dogs met the criteria for inclusion in the study. Dogs were included in the study if they had clinical signs suggestive of DM in combination with persistent hyperglycemia and glucosuria or persistent hyperglycemia despite insulin treatment. 7,8 Inclusion in the study also required a calculated osmolality ≥ 325 mOsm/kg at the time of initial examination. Exclusion criteria consisted of insufficient data for a diagnosis of DM, incomplete medical record, erroneous coding of dogs as diabetic, or a calculated osmolality that was < 325 mOsm/kg. A medical record was defined as complete if it included a detailed history, physical examination findings, serum biochemistry screen, and repeated blood glucose concentration measurements.

Procedures

Medical records of dogs included in the study were reviewed and signalment, clinical signs, physical examination findings, clinopathologic test results, urinalysis, aerobic culture of urine obtained by cystocentesis, endocrine test results, histopathology, ultrasonographic findings, outcome, and necropsy results were recorded.

Diabetic dogs with osmolality ≥ 325 mOsm/kg were defined as dogs with an HHS and were divided into 2 subgroups. One subgroup of dogs did not have ketonuria (HNK) and the other subgroup had ketonuria (HK). Data were analyzed for all dogs with HHS and also for the 2 HHS subgroups of dogs with HNK or HK. Data from the HNK and HK subgroups were compared to one another.

Physical examination findings

Physical examination findings were recorded from the time of initial examination. Body condition score (BCS) on a scale of 1-9 was used, and a BCS of 1 was assigned to dogs with cachexia, a BCS of 2-3 was classified as underweight, a BCS of 4-5 was considered normal, a BCS of 7-8 was considered overweight, and a BCS of 9 was assigned to obese dogs. Dehydration status was subjectively classified as mild, moderate, or severe. Fever was defined as a temperature above 39.4°C (103°F) in a quiet patient, and hypothermia was defined as temperature below 37.7°C (100°F). Neurologic status was reported as abnormal if the dog was subjectively assessed as depressed or dull, disoriented, obtunded, recumbent, or showed signs of ataxia, weakness, shaking, tremors, or seizures.

Clinicopathologic findings

Results of initial diagnostic tests were recorded in all dogs. Recorded clinicopathologic findings included a CBC, 9 serum biochemistry screen, 9 and venous blood gas analysis. 9 Lipemia was subjectively noted by the laboratory technician who handled the serum sample for the biochemistry screen. Calculated osmolality was reported as part of the initial serum biochemistry screen using the following formula: mOsm/kg = [2 × plasma [Na+]] mmol/L + [(glucose)/18] mg/dL + [(BUN)/2.8] mg/dL. Effective osmolality was also calculated with values obtained from the biochemistry screen using a different formula: mOsm/kg = [2 × plasma [Na+]] mmol/L + [(glucose)/18] mg/dL.

Urine was analyzed from the time of initial examination. 9 Urine was considered hyposthenuric,
isosthenuric, or hypersthenuric if the specific gravity was below 1.007, between 1.007 and 1.015, or above 1.015, respectively. Protein, ketones, bilirubin, urobilinogen, and hemoglobin were recorded as absent or present (+1 to +4) in urine. Aerobic urine bacterial culture was performed on urine obtained by cystocentesis at the time of initial examination. A dog was considered to have azotemia if it had a BUN concentration >11.8 mmol/L (33 mg/dL) or creatinine concentration above 159 µmol/L (1.8 mg/dL). Corrected sodium was calculated by adding 1.6 to the measured serum sodium for each 5.55 nmol/L (100 mg/dL) of glucose above 11.1 nmole/L (200 mg/dL).

**Endocrine testing**

Hyperadrenocorticism was diagnosed based on history, clinical signs, and adrenal function testing (eg, low-dose dexamethasone suppression test, adrenocorticotropic hormone stimulation test), as previously described.

**Imaging**

Abdominal ultrasonographic studies were performed at the teaching hospital at the time of initial examination and were reviewed by a board-certified radiologist at that time. Acute pancreatitis was suspected if a dog had clinical signs consistent with acute pancreatitis and ultrasonographic findings of an enlarged, irregular, and hypoechoic pancreas with hyperechoic peripancreatic mesentery.

**Outcome**

A positive outcome was defined as discharge from the hospital. A negative outcome was defined as death, by euthanasia or as the dog succumbed to disease.

**Statistical analysis**

Continuous variables were assessed for normality using the Shapiro-Wilks test. Mean ± SD was used to describe normally distributed variables while median and range were applied to not normally distributed variables. The t-test or Wilcoxon rank-sum test was used to compare continuous variables between groups depending on whether they were normally or not normally distributed, respectively. Categorical variables were described using percent and the chi-square test or Fisher’s exact test (if the expected count within any of the cells was <0.05) was used to compare these variables between groups. A P value <0.05 was considered significant for all evaluations. All statistical analyses were performed using a statistical software package.

**Results**

HHS was diagnosed in 66 of 1,250 (5%) diabetic dogs examined at the teaching hospital during the study period. Thirty-four of 66 dogs with HHS (51%) had HK, 25 of 66 HHS dogs (38%) had HNK, and the remaining 7 of 66 HHS dogs (11%) did not have a urinalysis performed.

Mean (±SD) age of all dogs with HHS at the time of the hyperosmolar episode was 9.7 ± 3.1 years. Mean age of dogs at the time of the hyperosmolar episode was not significantly different between the HK and HNK dogs (9.0 ± 3.2 y and 10.1 ± 2.7 y, respectively). Mean age of all dogs with HHS at the time of diagnosis of DM was 8.7 ± 3.5 years. Mean age of dogs at the time of diagnosis of DM was not significantly different between the HK and HNK dogs (8.1 ± 3.6 y and 8.9 ± 3.3 y, respectively). Age was not associated with outcome.

Thirty-five of 66 (53%) HHS dogs were neutered male dogs, 24 (36%) were neutered female dogs, 4 (6%) were intact female dogs, and 3 (4%) were intact male dogs. There was no significant difference in sex distribution of dogs with HK compared to dogs with HNK. Fourteen (21%) of the 66 dogs with HHS were of mixed breeding, 6 (9%) dogs each were Miniature Poodles, Yorkshire Terriers, or Malteses, 5 (8%) were Bichon Frises, 4 (6%) were Miniature Schnauzers, 3 (4%) were Toy Poodles, 2 each (3%) were Labrador Retrievers, Rottweilers, or Dachshunds, and others were one each of various additional pure breeds.

Within the group of 66 dogs with HHS, 35 dogs (53%) were newly diagnosed diabetics that had not been previously treated with insulin. Thirty-one (47%) dogs with HHS had been previously diagnosed as diabetic and had been treated with insulin for a median of 12 months (range 0.03–108 months). There was no significant difference in the number of dogs that received insulin treatment prior to examination or in duration of prior insulin treatment between the HK and HNK groups.

Mean duration of clinical signs prior to the hyperosmolar episode was 0.30 ± 0.39 months (range 0.03–3 mo) in all 66 HHS dogs. Clinical signs included inappetence (documented in 63 of 66 dogs, 95%), lethargy (61, 92%), vomiting (58, 88%), polyuria and polydipsia (44, 67%), owner-reported behavioral changes (29, 44%), and diarrhea (18, 27%). Blood glucose concentration was above 3.6 mmol/L (65 mg/dL) in all dogs with behavioral changes.

Mean duration of clinical signs prior to the hyperosmolar episode in 34 dogs with HK was 0.20 ± 0.14 months (range 0.03 to 0.5 months). The most common clinical signs observed in dogs with HK were vomiting (32 of 34, 94%), lethargy (31, 91%), inappetence (31, 91%), polyuria and polydipsia (26, 76%), diarrhea (12, 35%), and behavioral changes (12, 35%).
Mean duration of clinical signs prior to the hyperosmolar episode in 25 dogs with HNK was 0.38 ± 0.57 months (range 0.03–3 mo). The most common clinical signs observed in dogs with HNK were inappetence and lethargy (observed in 25 of 100% and 24, 96%, respectively), vomiting (20, 80%), polyuria and polydipsia (13, 52%), behavioral changes (15, 60%), and diarrhea (3, 12%). Dogs with HK had a significantly shorter duration of clinical signs than dogs with HNK (P = 0.02). There was no significant association between a history of behavioral changes and outcome, nor was there a significant difference in the number of dogs that had behavioral changes in the HNK and HK groups.

Twenty of 66 (30%) HHS dogs in which subjective body condition was recorded were thought to have normal body condition, 19 (29%) were considered to be overweight, 16 (24%) were underweight, and 9 (14%) were obese. Median body weight for 66 dogs with HHS was 8.4 kg (range 2.1–52 kg). Moderate to severe dehydration was noted in 57 of 66 (86%) dogs with HHS. Presence of moderate to severe dehydration was not significantly different between HK (28 of 34, 82%) and HNK groups (23 of 25, 92%), and there was no significant association between dehydration and outcome.

Median body temperature for all HHS dogs was 38.6 °C (range 35.6–41 °C) [101.4 °F (range 96–105.8 °F)]. Seven of 66 dogs (11%) had a body temperature >39.4 °C (>103.0 °F), while 13 dogs (20%) had body temperatures <37.7 °C (<100 °F). Dogs with HK had a significantly higher body temperature (median 39 °C (102.2 °F), range 35.6–41 °C [96–105.8 °F]) than those with HNK (median 38.2 °C (range 35.8–40.1 °C) [100.8 °F (range 96.5–104.2 °F)], although the median body temperature in both groups was within the normal range (P = 0.006). Body temperature was not associated with outcome.

Mental status was recorded by the attending clinician in 66 dogs with HHS. Forty-eight (73%) of the dogs with HHS were found to have abnormal mentation that included dull or depressed mentation (42 dogs, 64%) or coma (6 dogs, 9%). Abnormal mental status was associated with a poor outcome (P = 0.03). Coma, which was identified in 3 dogs with HNK, 2 dogs with HK, and 1 dog with unclassified HHS, was also associated with a poor outcome (P = 0.03), and specifically with euthanasia (P = 0.01). Five of the 6 dogs that had coma died. HK dogs were not significantly more likely to have abnormal mentation noted by the attending clinician (28 of 35, 80%) than HNK dogs (15 of 25, 60%). There was no significant association between the presence of behavioral changes or abnormal neurologic physical examination findings and calculated or effective osmolality, BUN, sodium, or glucose concentrations. Additional physical examination findings were cranial organomegaly (25 of 66 dogs, 38%), painful abdomen (23, 35%), and respiratory abnormalities, most often reported as increased respiratory rate and effort (21, 32%).

Results of CBCs, serum biochemistry findings, and venous blood gas analyses are presented in Tables 1–3. The only CBC variable that was significantly different between the HK and HNK groups was the total WBC count that was significantly higher in the HK compared to the HNK group (P = 0.01).

Most serum biochemistry findings were also not significantly different between the HK and HNK groups (Table 2). The only biochemical variables that were significantly different were BUN, creatinine, and potassium concentrations, as well as calculated osmolality that were significantly higher in the HK group compared to the HNK group (P = 0.0002, P = 0.008, P = 0.009, and P = 0.001, respectively). However, effective osmolality was significantly higher in the HK group compared to the HNK group (P = 0.02). Outcome was not significantly associated with WBC count, BUN, sodium, corrected sodium, or glucose concentrations, nor was it associated with calculated or effective osmolality. Lipemia was subjectively noted in 13 of 66 dogs (20%) with HHS, including 8 of 34 dogs (23%) with HK and 5 of 25 dogs (20%) with HNK.

Venous pH, lactate, and bicarbonate concentrations were not significantly different between the HK and HK groups (Table 3). However, mean venous pH was associated with outcome, and was significantly lower in dogs that did not survive to discharge (7.24 ± 0.13) compared to those that were discharged from the hospital (7.30 ± 0.09, P = 0.045).

A urinalysis was performed in 59 of 66 dogs with HHS. Thirty-six dogs (61%) had hypersthenuria, 21 (36%) had isosthenuria, and 2 (3%) had hyposthenuria. Forty-nine dogs (83%) had proteinuria, 48 (81%) had glucosuria, 43 (73%) had hemoglobinuria, 34 (58%) had ketonuria, 27 (46%) had bilirubinuria, and none had more than 5 WBC/Hpf.

Aerobic urine culture was performed in 58 of 66 (88%) HHS dogs. Fourteen of 58 (24%) showed bacterial growth on urine culture; *Escherichia coli* was the most common isolate either as a single or mixed infection. Seven of the 14 dogs with a urinary tract infection (UTI) had HNK, 5 dogs had HK, and 2 were unclassified. There was no significant difference between the HNK and HK groups with respect to presence of UTI, and UTI was not associated with outcome.

Abdominal ultrasound was performed on 55 of 66 dogs (83%), and the most common abnormality reported was acute pancreatitis. Acute pancreatitis was diagnosed in 24 of 66 (36%) dogs with HHS-based on clinical signs and abdominal ultrasonographic findings. Acute pancreatitis was diagnosed in 17 of 34 dogs (50%) with HK, 6 of 25 dogs (24%) with HNK, and in 1 of 7 dogs (14%)
with unclassified HHS. Dogs with HK were significantly more likely to have acute pancreatitis compared to dogs with HNK ($P = 0.046$). Acute pancreatitis was not significantly associated with outcome.

Adrenal axis testing was performed in 25 of 66 (38%) dogs with HHS that had clinical signs, physical examination findings, and clinicopathologic abnormalities consistent with a diagnosis of hyperadrenocorticism. Adrenal axis testing confirmed a diagnosis of hyperadrenocorticism in 12 of 66 (18%) dogs with HHS. Six of these 12 dogs had HNK, 4 dogs had HK, and 2 had unclassified HHS. There was no significant difference between the HNK and HK groups with respect to having hyperadrenocorticism. Seven of the 12 dogs that had hyperadrenocorticism were diagnosed with hyperadrenocorticism prior to the hyperosmolar episode, and 5 dogs were diagnosed with hyperadrenocorticism after resolution of the HHS episode. Outcome was not associated with a diagnosis of hyperadrenocorticism.

Neoplasia was not histologically or cytologically confirmed in any of the dogs, although 1 dog had multiple mammary masses and an anal sac mass, and another dog had abdominal ultrasonographic evidence of an adrenal mass invading the caudal vena cava.

The most commonly administered medications prior to referral, other than insulin, were glucocorticoids (dexamethasone or prednisone). Twelve dogs received glucocorticoids for more than 7 days prior to examination for a variety of conditions including immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, cataract surgery, unspecified lameness, and suspected (and thereafter refuted) iatrogenic hypoadrenocorticism. Of the 12 dogs that received glucocorticoids prior to initial examination, 5 had HK, 6 had HNK, and 1 had unclassified HHS. Six additional dogs received a short course of glucocorticoid treatment just prior to referral.

Forty-one of 66 HHS dogs (62%) were discharged from the hospital. Of the 25 dogs (38%) with HHS that were not discharged from the hospital, 22 were euthanized and 3 died in the hospital. Twelve of the 25 dogs that did not survive (48%) had HNK, 11 (44%) had HK, and 2 dogs (8%) had unclassified HHS. Survival was not significantly different between the HK and HNK groups.

Postmortem examinations were performed in 7 dogs. Findings included severe acute necrotizing pancreatitis (identified in 2 dogs), severe nephropathy, hypertensive vasculopathy and cerebral malacia (1 dog), moderate multifocal acute to subacute renal tubular necrosis (1 dog), bilateral adenocortical adenomas and severe chronic interstitial nephritis (1 dog), brain tumor (1 dog), and multifocal unilateral subacute polioencephalomalacia with fibrinoid necrosis of blood vessels, gliosis, and histiocytosis (1 dog).

Discussion

HHS is a rare diabetic complication that affects about 5% of diabetic dogs and carries a guarded to poor prognosis, as only 62% of dogs survived. The prognosis of dogs with HK was similar to that of dogs with HNK, and poor outcome was not associated with age, WBC count, presence of acute pancreatitis or hyperadrenocorticism, osmolality, or BUN, sodium, and glucose concentrations.
Table 2: Serum biochemistry findings in 66 dogs with HHS and in the subgroups of dogs with HK DM (*n* = 34) or HNK DM (*n* = 25)∗

<table>
<thead>
<tr>
<th>Variable</th>
<th>HHS median</th>
<th>HHS range</th>
<th>HK median</th>
<th>HK range</th>
<th>HNK median</th>
<th>HNK range</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L; mg/dL)</td>
<td>37.7 (679)</td>
<td>2.8–80.9</td>
<td>38.5 (694)</td>
<td>11.5–73.8</td>
<td>30.4 (548.5)</td>
<td>3.9–47.5</td>
<td>3.6–6.5</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>33.7 (1084)</td>
<td>5.0–109.6</td>
<td>27.5 (1071)</td>
<td>5.0–72.8</td>
<td>61.2 (171.5)</td>
<td>5.0–109.6</td>
<td>1.8–10.7</td>
</tr>
<tr>
<td>Creatinine (μmol/L; mg/dL)</td>
<td>300.6 (300.6)</td>
<td>7.6–1211.1</td>
<td>221 (147)</td>
<td>7.6–671.8</td>
<td>389 (181.5)</td>
<td>7.6–937</td>
<td>61.9–159.1</td>
</tr>
<tr>
<td>Phosphorus (mmol/L; mg/dL)</td>
<td>2.5 (8.85)</td>
<td>0.2–10.5</td>
<td>1.7 (5.3)</td>
<td>0.2–9.2</td>
<td>3.1 (9.6)</td>
<td>0.6–10.5</td>
<td>0.9–2.0</td>
</tr>
<tr>
<td>Total calcium (mmol/L; mg/dL)</td>
<td>33.7 (8.95)</td>
<td>1.3–3.1</td>
<td>2.2 (8.7)</td>
<td>1.3–3.1</td>
<td>1.8–10.7</td>
<td>1.3–3.1</td>
<td>2.4–2.9</td>
</tr>
<tr>
<td>Sodium (mmol/L; mEq/L)</td>
<td>144 (144)</td>
<td>120–185</td>
<td>148 (144)</td>
<td>121–175</td>
<td>143 (144)</td>
<td>132–185</td>
<td>140–150</td>
</tr>
<tr>
<td>Corrected sodium (mmol/L; mEq/L)</td>
<td>151 (151)</td>
<td>134–183</td>
<td>156 (156)</td>
<td>134–179</td>
<td>149 (156)</td>
<td>134–183</td>
<td>140–150</td>
</tr>
<tr>
<td>Potassium (mmol/L; mEq/L)</td>
<td>4.5 (3.9)</td>
<td>2.3–7.0</td>
<td>3.7 (3.9)</td>
<td>2.3–6.4</td>
<td>5.0 (5.0)</td>
<td>3.9–7.0</td>
<td>3.9–4.9</td>
</tr>
<tr>
<td>Chloride (mmol/L; mEq/L)</td>
<td>108 (108)</td>
<td>58–155</td>
<td>111 (111)</td>
<td>58–143</td>
<td>105.5 (105.5)</td>
<td>58–155</td>
<td>109–120</td>
</tr>
<tr>
<td>Total CO₂ (mmol/L)</td>
<td>13 (13)</td>
<td>5.0–109.6</td>
<td>27.5 (27.5)</td>
<td>5.0–72.8</td>
<td>61.2 (61.2)</td>
<td>5.0–109.6</td>
<td>1.8–10.7</td>
</tr>
<tr>
<td>Total protein (g/L; g/dL)</td>
<td>59 (5.9)</td>
<td>34–83 (3.4–8.3)</td>
<td>57 (5.7)</td>
<td>34–83 (3.4–8.3)</td>
<td>56 (5.6)</td>
<td>34–83 (3.4–8.3)</td>
<td>54–71 (5.4–7.1)</td>
</tr>
<tr>
<td>Albumin (g/L; g/dL)</td>
<td>30 (3.0)</td>
<td>15–49 (1.5–4.9)</td>
<td>29 (2.9)</td>
<td>15–49 (1.5–4.9)</td>
<td>32 (3.2)</td>
<td>20–42 (2.0–4.2)</td>
<td>25–37 (2.5–3.7)</td>
</tr>
<tr>
<td>Globulins (g/L; g/dL)</td>
<td>28 (2.8)</td>
<td>15–42 (1.5–4.2)</td>
<td>28 (2.8)</td>
<td>15–42 (1.5–4.2)</td>
<td>37 (2.7)</td>
<td>19–39 (1.9–3.9)</td>
<td>24–40 (2.4–4.0)</td>
</tr>
<tr>
<td>ALT (U/L; units/L)</td>
<td>79 (79)</td>
<td>18–650 (18–650)</td>
<td>79 (79)</td>
<td>18–285 (18–285)</td>
<td>94.5 (94.5)</td>
<td>51–281 (51–281)</td>
<td>16–91 (16–91)</td>
</tr>
<tr>
<td>AST (U/L; units/L)</td>
<td>1125 (1125)</td>
<td>179–2818</td>
<td>1125 (1125)</td>
<td>179–2818</td>
<td>1125 (1125)</td>
<td>179–2818</td>
<td>20–155</td>
</tr>
<tr>
<td>GGT (U/L; units/L)</td>
<td>17 (17)</td>
<td>7–191 (7–191)</td>
<td>17 (17)</td>
<td>7–191 (7–191)</td>
<td>17 (17)</td>
<td>7–191 (7–191)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L; mg/dL)</td>
<td>10.3 (0.6)</td>
<td>5.1–31.3</td>
<td>10.3 (0.6)</td>
<td>5.1–31.3</td>
<td>10.3 (0.6)</td>
<td>5.1–31.3</td>
<td>3.3–8.2</td>
</tr>
<tr>
<td>Cholesterol (mmol/L; mg/dL)</td>
<td>8.2 (324)</td>
<td>2.6–16.9 (102–653)</td>
<td>8.4 (324)</td>
<td>3.1–20.0 (119–773)</td>
<td>7.7 (287)</td>
<td>2.6–13.7 (102–528)</td>
<td>3.3–8.2</td>
</tr>
<tr>
<td>Calculated osmolality (mOsm/kg)</td>
<td>341 (341)</td>
<td>325–382</td>
<td>339 (339)</td>
<td>325–382</td>
<td>352 (352)</td>
<td>325–382</td>
<td>322–308</td>
</tr>
<tr>
<td>Effective osmolality (mOsm/kg)</td>
<td>327 (327)</td>
<td>276–381</td>
<td>335 (335)</td>
<td>276–381</td>
<td>315 (315)</td>
<td>276–374</td>
<td>292–308</td>
</tr>
</tbody>
</table>

∗These variables were significantly different between HK and HNK dogs.

HHS, hyperosmolar hyperglycemic state; HK, hyperosmolar ketonuric; HNK, hyperosmolar nonketonuric; DM, diabetes mellitus.

Table 3: Venous blood gas findings in 66 dogs HHS and in the subgroups of dogs with HK DM (*n* = 34) or HNK DM (*n* = 25)∗

<table>
<thead>
<tr>
<th>Variable</th>
<th>HHS median</th>
<th>HHS range</th>
<th>HK median</th>
<th>HK range</th>
<th>HNK median</th>
<th>HNK Range</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous pH</td>
<td>7.3 (7.3)</td>
<td>6.926–7.487</td>
<td>7.28 (7.28)</td>
<td>6.93–7.46</td>
<td>7.27 (7.27)</td>
<td>7.058–7.432</td>
<td>7.35–7.47</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L; mEq/L)</td>
<td>15.7 (15.7)</td>
<td>5.9–30.8</td>
<td>14.9 (14.9)</td>
<td>5.9–25</td>
<td>17.0 (17.0)</td>
<td>5.9–25.2</td>
<td>20–24</td>
</tr>
<tr>
<td>Lactate (mmol/L; mg/dL)</td>
<td>2.9 (26.1)</td>
<td>0.4–7.8</td>
<td>3.0 (27.0)</td>
<td>0.8–6.0</td>
<td>2.2 (19.8)</td>
<td>0.4–7.8</td>
<td>0–2.5</td>
</tr>
</tbody>
</table>

∗None of the variables were significantly different between HK and HNK dogs.

HHS, hyperosmolar hyperglycemic state; HK, hyperosmolar ketonuric; HNK, hyperosmolar nonketonuric; DM, diabetes mellitus.

Poor outcome was associated only with abnormal mental status, coma, and low venous pH.

Abnormal mental status is common in people with HHS and is attributed to osmotic shifts. Hyperglycemia and osmotic diuresis lead to severe dehydration, free water loss, and hyperosmolality of the extracellular fluid space. Increased extracellular fluid glucose concentration causes an osmotic shift of water out of the cells, leading to intracellular fluid loss. Cellular dehydration in the central nervous system causes neurologic abnormalities and in extreme cases, coma. In people, there is a correlation between severity of osmolality and degree of mental alteration. However, an association between osmolality and abnormal mentation was not documented in the present study, possibly due to small sample size. Although dogs with abnormal mentation had a significantly worse outcome than other dogs, as has been reported in humans with HHS, this finding must be interpreted with caution.
and a poor outcome, it is also possible that owners of comatose dogs were more likely to have the dog euthanized due to a perceived poor outcome.

Behavioral changes were reported in 12 (35%) dogs with HK and 15 (60%) dogs with HNK. Although there was no significant difference in the number of dogs that had behavioral changes in the HK and HNK groups or in abnormal mentation noted by the attending clinician, the numbers analyzed are small, and future larger studies may find that dogs with HNK have more neurologic clinical signs than dogs with HK.

Hyperosmolality was an important inclusion criterion in this study and was defined at a relatively high cutoff to ensure that all of the dogs studied did indeed have HHS. A cutoff of calculated serum osmolality greater than 325 mOsm/kg was chosen, based on current literature. Normal effective serum osmolality has been studied in 20 healthy, mature, well-hydrated dogs (10 female and 10 male) and was found to range from 292 to 308 mOsm/kg with a mean of 301 mOsm/kg. When dehydration was induced in these same normal dogs by withholding water for as long as 96 hours or until clinical dehydration was apparent, maximal serum osmolality ranged from 296 to 331 mOsm/kg with a mean of 315 mOsm/kg. Other smaller studies of normal well-hydrated dogs have reported a mean serum osmolality of 309–311 mOsm/kg. A study of 14 diabetic dogs defined hyperosmolality as an osmolality > 310 mOsm/kg, and marked hyperosmolality, identified in 3 dogs, as that > 330 mOsm/kg. The American Diabetes Association defines hyperosmolality in human diabetics as an effective serum osmolality > 320 mOsm/kg. Therefore, a calculated serum osmolality greater than 325 mOsm/kg seemed like a high enough cutoff that would ensure that only dogs with HHS were included in the study.

Over half of the dogs with HHS were newly diagnosed diabetics that had not received prior insulin treatment. This finding is similar to that observed in dogs with DKA and in people with either DKA or HHS. It is therefore concluded that development of HHS in dogs may be attributed, in part, to untreated or poorly-regulated diabetics.

Mean reported duration of clinical signs prior to the hyperosmolar episode was relatively short (0.30 ± 0.39 mo). This is unexpected, especially for the 31 dogs that had been previously diagnosed as diabetic and treated with insulin for a median of 12 months. It is possible that dog owners had come to accept the presence of some clinical signs, such as polyuria and polydipsia (reported in 44 dogs), and that these clinical signs had been ongoing for more than 0.3 months, whereas the onset of other clinical signs, such as inappetence (reported in 63 dogs), was acute and noticeable.

Some differences were noted between the HNK and HK subgroups. Dogs with HK were significantly more likely to have acute pancreatitis compared to dogs with HNK. Dogs with HK also had a significantly higher body temperature and WBC count compared to dogs with HNK and it is possible that these changes were due to acute pancreatitis. The shorter duration of clinical signs observed in dogs with HK compared to dogs with HNK, may also be attributed to the acute need for hospitalization due to the onset of acute pancreatitis.

Calculated osmolality was significantly higher in the HNK group compared to the HK group, whereas effective osmolality was significantly higher in the HK group compared to the HNK group. This difference may be explained by the fact that BUN concentration, which is taken into account only with calculated osmolality, was also significantly higher in the HNK compared to the HK group. The higher BUN concentration resulted in higher calculated, but not effective, osmolality in the HNK group. Other biochemical variables associated with decreased renal function including creatinine and potassium concentrations were also significantly higher in the HNK group compared to the HK group. Although outcome was not significantly associated with BUN, creatinine, or potassium concentration, all of which were significantly higher in dogs with HNK compared to dogs with HK, the numbers analyzed are small, and future larger studies may find that dogs with HNK have some degree of renal insufficiency that may affect their outcome following discharge from the hospital.

One of the limitations of this study is that 13 of 66 serum samples (20%) had lipemia, which can alter the reported concentration of some of the variables, including sodium and therefore also osmolality. Lipemia is common in diabetic dogs, and has been previously reported in 92 of 221 (42%) diabetic dogs, so exclusion of dogs with lipemia from a study focusing on diabetic dogs, is not warranted. However, it is possible that as technology improves, future biochemical analyzers that are able to overcome this difficulty may become more readily available.

Another study limitation is that 7 of 66 dogs with HHS did not have a urinalysis performed. Inclusion in the study required a calculated serum osmolality ≥ 325 mOsm/kg, with or without ketonuria. Since the presence or absence of ketonuria was not required for inclusion in the study, these dogs were included despite the fact that they did not have a urinalysis performed. These dogs were defined as having unclassified HHS because they could not be classified as having HK or HNK. It was decided to include these dogs in the study because it was theorized that exclusion of these dogs may bias the results of the study by excluding the most critically ill
dogs, in which a urinalysis could not be obtained due to severe dehydration or urgency of intense care over diagnostic evaluation. Indeed, 2 of 25 dogs (8%) that did not survive and 1 of 6 dogs (17%) with coma had unclassified HHS. However, the numbers are small and this rationale cannot be definitively confirmed. An additional study limitation is that in this retrospective study, degree of dehydration was determined subjectively, by a number of clinicians, and the criteria used by each clinician are unknown.

Venous pH was not significantly different between the HNK and HK groups, although it may have been expected that ketonuria, present in dogs with HK, could lower the venous pH. This retrospective study is limited by the fact that serum beta-hydroxybuterate was not available for review in the medical records. Future prospective studies in which serum beta-hydroxybuterate is measured may be able to investigate an association between degree of acidosis and degree of ketosis in dogs with HK.

In conclusion, the definition of canine HHS based on a calculated serum osmolality \( \geq 325 \) mOsm/kg identifies a population of dogs with a rare diabetic complication that carries a guarded prognosis. Outcome is associated with abnormal mental status and a low venous pH. Dogs with HK were significantly more likely to have acute pancreatitis, higher body temperature and WBC count, and also to have a shorter duration of clinical signs. Dogs with HNK had significantly more azotemia and higher calculated osmolality.

**Footnotes**

- a Hematology analyzer, Celldyne 3500, Abbott Laboratories, Abbott Park, IL.
- b Chemistry analyzer, Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY.
- c Stat Profile, NOVA Biomedical Corporation, Waltham, MA.
- d Urinalysis N-Multistix SG, Bayer Corporation, Elkhart, IN.
- e Intercooled Stata 7.0 for Windows, College Station, TX.

**References**