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Glycemic control in dogs with DM may be complicated, in part, by concurrent disorders. Concurrent disorders are thought to cause insulin resistance and are believed to be present in most dogs that develop diabetic ketoacidosis (DKA). It has been suggested that concurrent disorders contribute to an increase in concentrations of counter-regulatory hormones (e.g., glucagon, catecholamines, glucocorticoids, and growth hormone) and a hormonal imbalance that is involved in the pathogenesis of DKA. In addition, inadequate glycemic control in dogs with DM may result in decreased neutrophil adherence, which may predispose these dogs to various infections.

Because of the advanced age of most dogs with DM, it is possible that many have concurrent disorders at the time DM is diagnosed. The purpose of the study reported here was to identify concurrent disorders in dogs with DM and determine which occur most frequently. Knowledge of the most common concurrent disorders in diabetic dogs may help focus diagnostic evaluations, and recognition of these disorders may improve treatment of diabetic dogs and may prevent insulin resistance or DKA in some dogs.

Criteria for Selection of Cases
A computer search of the medical records of all dogs admitted to the Veterinary Hospital of the University of Pennsylvania between January 1993 and May 1998 was performed, and dogs in which DM had been diagnosed were identified. Medical records of dogs in which DM had been diagnosed were reviewed in detail by a board-certified veterinary internist (RSH). 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.

Procedures
Medical records of dogs included in the study were reviewed, and signalment, clinical signs, physical examination findings, and results of clinicopathologic testing, urinalysis, aerobic bacterial culture of urine samples, coagulation testing, endocrine testing, histologic evaluation, diagnostic imaging, and necropsy findings were recorded.

Physical examination findings—Results of physical examination performed at the time of initial examination at the veterinary teaching hospital were recorded. Body condition was subjectively classified as overweight, normal, or underweight. Hydration status was classified as good, fair, or poor. Fever was defined as a rectal temperature > 39.4 C (103 F), and hypothermia...
were considered prolonged if they were
 ing and interpreting results of
 protocols were used for perform-
 was considered increased if it was
 was subjectively evaluated for lipemia.
 and 1.015, or
 concentration was measured at the time of initial examination at the veterinary teaching hospital were submitted for aerobic analyses of urine for protein, ketones, glucose, bilirubin, urobilinogen, and hemoglobin were recorded (absent or present). Urine samples obtained by means of cystocentesis at the time of initial examination at the veterinary teaching hospital were submitted for aerobic bacterial culture.

Coagulation testing—Results of coagulation tests performed at the time of initial examination at the veterinary teaching hospital were recorded. Partial thromboplastin time (PTT) and prothrombin time (PT) were considered prolonged if they were >125% of the control value. Concentration of fibrin split products (FSP) was considered increased if it was >10 µg/dl. Platelet count was considered decreased if it was <175,000/µl.

Endocrine testing—Hyperadrenocorticism (HAC) was diagnosed on the basis of history, clinical signs, results of adrenal function testing, or histologic evaluation. Standard protocols were used for performing and interpreting results of low-dose dexamethasone suppression (LDDS) tests. A plasma cortisol concentration >1 µg/dl 8 hours after administration of dexamethasone (0.01 mg/kg, IV) or ≥ 22 µg/dl 2 hours after administration of adrenocorticotropic hormone (ACTH; 2.2 U/kg, IM) was considered consistent with a diagnosis of HAC. A low baseline serum thyroxine (T₄) concentration with inadequate response to administration of thyroid stimulating hormone (TSH) or a low total T₄ concentration (<15 nmol/L or 1.2 µg/dl) in conjunction with a high TSH concentration (>30 mU/L) was considered consistent with a diagnosis of hypothyroidism. For the TSH stimulation test, dogs received 1 unit of TSH, IV, if they weighed <20 kg and 2 units, IV, if they weighed ≥20 kg. Serum T₄ concentration was measured before and 6 hours after administration of TSH. Response time of TSH was considered inadequate if serum T₄ concentration 6 hours after administration of TSH was less than twice the baseline concentration, with an absolute increase of <2 µg/dl. Dogs treated with thyroid hormone supplementation in which endocrine testing or histologic analysis had not been done to confirm the diagnosis were not considered hypothyroid.

Histologic evaluation—Results of necropsies and of all histologic evaluations of biopsy and necropsy specimens performed at the veterinary teaching hospital were recorded; all biopsy and pathology reports had been reviewed by a board-certified pathologist at the time the biopsy evaluation or necropsy had been performed. For the present study, histologic findings for dogs with pancreatic abnormalities were reviewed an additional time by a board-certified pathologist (TVW). Biopsy and pathology reports were reviewed and summarized by a board-certified internist (RSH). Two histologic forms of acute pancreatitis were identified: acute pancreatic necrosis and acute pancreatic necrosis with fibrosis. Acute pancreatic necrosis was defined as moderate to severe acute pancreatic acinar and peripancreatic fat necrosis with a minimal to moderate inflammatory infiltrate of neutrophils and macrophages. Intersitial fibrosis was minimal to mild in these dogs. Acute pancreatic necrosis with fibrosis was defined as similar necrosis with extensive preexisting intersitial fibrosis and infiltration of lymphocytes and plasma cells. Dogs with chronic fibrosing nonsuppurative pancreatitis without necrosis were not considered to have acute pancreatitis.

Diagnostic imaging—Results of all radiographic and abdominal ultrasonographic examinations performed at the time of initial examination at the veterinary teaching hospital were recorded. All examinations had been reviewed by a board-certified radiologist at the time they had been performed. For the present study, results of radiographic and ultrasonographic examinations of the pancreas were reviewed an additional time by a board-certified radiologist (HMS), who specifically examined abdominal radiographs for increased radiopacity and loss of detail in the right cranial quadrant, abnormal displacement of the descending duodenum or stomach, and gas in the descending duodenum. Acute pancreatitis was suspected if increased radiopacity and loss of detail in the area of the right cranial quadrant were observed or if the descending duodenum was displaced and gas-filled. Abdominal ultrasonograms were evaluated for pancreatic size, pancreatic border definition, pancreatic echogenicity, peripancreatic mesenteric echogenicity, peritoneal effusion, and signs of duodenitis (gas-filled, thickened duodenum). Acute pancreatitis was suspected if the pancreas was hypoechoic and the peripancreatic mesentry was hyperechoic. Reports of radiographic and ultrasonographic studies were then reviewed and summarized by a board-certified internist (RSH). Radiographic and ultrasonographic abnormalities were reported only if they were observed in >1 dog.
Data analysis—Data are given as mean ± SD, median and range, or frequencies and percentages.

Results
Medical records of 295 dogs in which DM had been diagnosed were reviewed, and 221 dogs met the criteria for inclusion in the study. Of these, 174 (79%) had clinical signs suggestive of DM in conjunction with persistent hyperglycemia and glucosuria, and 47 (21%) had clinical signs suggestive of DM in conjunction with persistent hyperglycemia despite treatment with insulin.

Mean ± SD age of the dogs at the time DM was diagnosed was 8.9 ± 2.9 years (median, 7 years; range, 3 months to 16 years). Eighty-nine (40.3%) dogs were neutered females, 78 (35.3%) were neutered males, 38 (17.2%) were sexually intact males, and 16 (7.2%) were sexually intact females. Fifty-eight (26%) of the dogs were mixed-breeds, 27 (12%) were Miniature Poodles, 11 (5%) were Samoyeds, 9 (4%) were Toy Poodles, 7 (3%) were Yorkshire Terriers, 7 (3%) were Rottweilers, 6 (3%) were Lhasa Apsos, and 5 (2%) were Pugs; the remainder represented a variety of breeds.

Duration of clinical signs prior to diagnosis of DM was reported for 126 dogs. Mean duration of clinical signs in these dogs was 1.3 ± 1.9 months (median, 0.75 months; range, 0.25 to 12 months). One hundred eighty-two (82%) dogs had polyuria and polydipsia, 125 (57%) had lethargy, 99 (43%) had inappetence or anorexia, 89 (40%) had weight loss, 48 (22%) had polyphagia, 28 (13%) had diarrhea, 8 (4%) had hematuria, 6 (3%) had weight gain, and 1 (0.5%) had polykurtia.

Most dogs (107, 48%) were subjectively assessed as overweight; 72 (33%) had normal body condition, and 42 (19%) were assessed as underweight. Most dogs (110, 50%) were well hydrated; 71 (32%) were moderately dehydrated, and 40 (18%) were severely dehydrated. Mean rectal temperature was 38.8 ± 0.6 °C (101.9 ± 1.2 °F), and median rectal temperature was 38.9 °C (101.9 °F) with a range of 35.5 to 40.8 °C (96 to 105.4 °F). Most dogs (176, 80%) had a normal rectal temperature; 35 (16%) had a fever, and 10 (4%) had hypothermia. One hundred thirty-five (61%) dogs had hepatomegaly, 58 (26%) had cataracts, and 58 (26%) had a cardiac murmur. Thirty-six (16%) dogs had dermatitis or otitis; 12 had dermatitis alone, 16 had otitis alone, and 8 had dermatitis and otitis. Twenty-three (10%) dogs had alopecia; 17 (8%) had palpable masses; 13 (6%) had dyspnea, coughing, or abnormal lung sounds; 13 (6%) had an orthopedic problem; and 13 (6%) had seizures. Seizures were observed in 7 dogs with hypoglycemia and 6 dogs with normal or high blood glucose concentration.

For most dogs, results of CBC performed at the time of initial examination at the veterinary teaching hospital were normal (Table 1). Most dogs had hyperglycemia at the time of initial examination (Table 2). Seven (3.2%) dogs had insulin-induced hypoglycemia, and 23 (11.3%) dogs had normoglycemia at the time of initial examination. However, all these dogs were later documented to have persistent hyperglycemia despite insulin treatment. Ionized calcium concentration was normal in <50% of the dogs. Most dogs with abnormal ionized calcium concentration had hypocalcemia. Mean ± SD ionized calcium concentration for the 41 hypocalcemic dogs was 0.97 ± 0.14 mmol/L (median, 1.02 mmol/L). Alkaline aminotransferase (ALT) and aspartate aminotransferase (AST) activities as well as alkaline phosphatase (ALP) activity were high in most dogs, whereas γ-glutamyltransferase (GGT) activity and total bilirubin and cholesterol concentrations were normal in most dogs. Amylase and lipase activities were high in more than half the dogs with DM. Calculated osmolarity was low in most dogs, and venous pH was low in 46% of dogs with DM. Ninety-two (42%) dogs had subjectively lipemic serum.

Most dogs (165, 81.3%) had hyperkalemia; 33 (16.3%) had hypokalemia, and 5 (2.4%) had normokalemia. Most dogs (179, 90%) had urine pH between 5 and 7.5, but 20 (10%) had a urine pH > 7.5; none of the dogs had a urine pH < 5. One hundred seventy-four (83%) dogs had glucosuria, 108 (52%) had proteinuria, 91 (44%) had hemoglobinuria, 73 (36%) had ketonuria, and 65 (31%) had bilirubinuria; all dogs had some urobilinogen in the urine. Most dogs (143, 91%) had ≤ 5 WBC in the urine sediment/high-power field (HPF); 14 (9%) dogs had > 5 WBC/HPF.

### Table 1—Results of CBC performed in dogs with diabetes mellitus

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. tested</th>
<th>No. with high value (%)</th>
<th>No. with normal value (%)</th>
<th>No. with low value (%)</th>
<th>Range</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (10⁶/µl)</td>
<td>202</td>
<td>5 (2)</td>
<td>135 (67)</td>
<td>62 (31)</td>
<td>2–9</td>
<td>5.5–8.2</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>201</td>
<td>6 (3)</td>
<td>142 (71)</td>
<td>53 (26)</td>
<td>4–28</td>
<td>12.6–19.1</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>212</td>
<td>6 (3)</td>
<td>155 (73)</td>
<td>51 (24)</td>
<td>11–65</td>
<td>36.9–55</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>201</td>
<td>13 (6.3)</td>
<td>181 (90)</td>
<td>7 (3.5)</td>
<td>57–97</td>
<td>62–75</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>198</td>
<td>11 (5.3)</td>
<td>178 (90)</td>
<td>9 (4.5)</td>
<td>27–47</td>
<td>31–38</td>
</tr>
<tr>
<td>Platelets (10⁹/µl)</td>
<td>55</td>
<td>19 (34.5)</td>
<td>25 (45.5)</td>
<td>11 (20)</td>
<td>0.005–790</td>
<td>1.75–4.00</td>
</tr>
<tr>
<td>WBC (cells/µl)</td>
<td>207</td>
<td>63 (30.4)</td>
<td>133 (64.3)</td>
<td>11 (5.3)</td>
<td>4,500–68,000</td>
<td>6,700–18,300</td>
</tr>
<tr>
<td>Neutrophils (cells/µl)</td>
<td>206</td>
<td>92 (45)</td>
<td>111 (54)</td>
<td>3 (1)</td>
<td>1,700–50,000</td>
<td>3,600–12,000</td>
</tr>
<tr>
<td>Band neutrophils</td>
<td>206</td>
<td>89 (43)</td>
<td>117 (57)</td>
<td>0</td>
<td>0–8,300</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes (cells/µl)</td>
<td>206</td>
<td>8 (4)</td>
<td>138 (67)</td>
<td>60 (29)</td>
<td>121–11,000</td>
<td>1,000–4,000</td>
</tr>
<tr>
<td>Monocytes (cells/µl)</td>
<td>206</td>
<td>30 (15)</td>
<td>141 (68)</td>
<td>35 (17)</td>
<td>0–14,000</td>
<td>100–1,500</td>
</tr>
<tr>
<td>Eosinophils (cells/µl)</td>
<td>206</td>
<td>3 (1)</td>
<td>102 (50)</td>
<td>101 (49)</td>
<td>0–2,990</td>
<td>50–1,500</td>
</tr>
</tbody>
</table>

*Platelet count was estimated in an additional 135 dogs and was considered adequate in 134 and low in 1.*
Eight (13%) dogs had proteinuria without hemoglobinuria, and bacterial culture of a urine sample did not yield any growth. Diabetic ketoacidosis was identified in 34 (15%) dogs that had ketonuria and a venous pH < 7.35.

Urine samples from 139 (72%) dogs were submitted for aerobic bacterial culture. Samples from 34 (21%) dogs yielded bacterial growth; the other 125 (79%) samples did not yield any growth. Escherichia coli was the most commonly isolated organism (18 dogs, 53%). It was the only organism isolated from 14 dogs; the other 4 dogs had a mixed bacterial infection.

Twenty-one (9.5%) dogs had a prolonged PTT or PT, a high FSP concentration, or a low platelet count. Partial thromboplastin and prothrombin times were measured in 42 dogs. Nine (4%) dogs had a prolonged PTT, PT, and FSP concentration. In 6, only the PTT was prolonged; in 1, only the PT was prolonged; and in 5, the PTT and the PT were prolonged. Concentration of FSP was measured in 40 dogs and was high in 3 (1%).

Table 2—Results of serum biochemical analyses in dogs with diabetes mellitus

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. tested</th>
<th>No. with high value (%)</th>
<th>No. with normal value (%)</th>
<th>No. with low value (%)</th>
<th>Range</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>221</td>
<td>189 (85.5)</td>
<td>25 (11.3)</td>
<td>7 (3.2)</td>
<td>19–1,330</td>
<td>67–147</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>208</td>
<td>45 (22)</td>
<td>155 (74)</td>
<td>8 (4)</td>
<td>1–307</td>
<td>5–30</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>208</td>
<td>56 (27)</td>
<td>140 (67)</td>
<td>12 (6)</td>
<td>0.3–10.6</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>208</td>
<td>41 (20)</td>
<td>157 (75)</td>
<td>10 (5)</td>
<td>0.6–32</td>
<td>2.2–6.0</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>208</td>
<td>2 (1)</td>
<td>120 (58)</td>
<td>86 (41)</td>
<td>5.2–12.4</td>
<td>9.7–12.2</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)</td>
<td>207</td>
<td>2 (1)</td>
<td>142 (69)</td>
<td>63 (30)</td>
<td>6.2–12.6</td>
<td>9.7–12.2</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>87</td>
<td>3 (3.5)</td>
<td>43 (49.4)</td>
<td>41 (47.1)</td>
<td>0.55–46</td>
<td>1.10–1.33</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>213</td>
<td>26 (12)</td>
<td>121 (57)</td>
<td>60 (31)</td>
<td>100–165</td>
<td>138–148</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>213</td>
<td>70 (33)</td>
<td>124 (58)</td>
<td>19 (9)</td>
<td>2.4–6.6</td>
<td>3.5–5.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>211</td>
<td>13 (6)</td>
<td>71 (34)</td>
<td>127 (60)</td>
<td>58–155</td>
<td>110–118</td>
</tr>
<tr>
<td>Carbon dioxide (mmol/L)</td>
<td>201</td>
<td>14 (7)</td>
<td>133 (66)</td>
<td>54 (27)</td>
<td>5–32</td>
<td>16–26</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>213</td>
<td>59 (28)</td>
<td>138 (65)</td>
<td>16 (7)</td>
<td>2.5–10.2</td>
<td>4.8–6.6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>207</td>
<td>17 (8)</td>
<td>173 (84)</td>
<td>17 (8)</td>
<td>1.3–5.5</td>
<td>2.3–3.9</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>208</td>
<td>163 (78)</td>
<td>45 (22)</td>
<td>0</td>
<td>12–1,371</td>
<td>3–50</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>110</td>
<td>78 (71)</td>
<td>32 (29)</td>
<td>0</td>
<td>18–1,386</td>
<td>1–37</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>208</td>
<td>188 (90)</td>
<td>20 (10)</td>
<td>0</td>
<td>32–6,160</td>
<td>20–155</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>103</td>
<td>24 (23)</td>
<td>79 (77)</td>
<td>0</td>
<td>6–386</td>
<td>5–25</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>208</td>
<td>57 (27)</td>
<td>151 (73)</td>
<td>0</td>
<td>0.1–11.1</td>
<td>0.1–0.7</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>207</td>
<td>69 (33)</td>
<td>136 (66)</td>
<td>2 (1)</td>
<td>102–1,165</td>
<td>126–259</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>73</td>
<td>37 (51)</td>
<td>36 (49)</td>
<td>0</td>
<td>314–19,219</td>
<td>&lt; 1,050</td>
</tr>
<tr>
<td>Lipase (U/L)</td>
<td>70</td>
<td>44 (63)</td>
<td>26 (37)</td>
<td>0</td>
<td>47–8,022</td>
<td>&lt; 1,500</td>
</tr>
<tr>
<td>Calculated osmolality</td>
<td>280</td>
<td>147 (59)</td>
<td>67 (24)</td>
<td>7 (3)</td>
<td>264–390</td>
<td>367–500</td>
</tr>
<tr>
<td>Venous pH</td>
<td>111</td>
<td>7 (6)</td>
<td>29 (26)</td>
<td>75 (68)</td>
<td>7.066–7.505</td>
<td>7.35–7.45</td>
</tr>
</tbody>
</table>

Hyperadrenocorticism was diagnosed in 51 (23%) dogs on the basis of history, clinical signs, and results of adrenal function testing (50 dogs) or on the basis of history, clinical signs, and results of histologic evaluation of necropsy specimens (1). Clinical signs suggestive of HAC consisted of polyuria and polydipsia (44 dogs), lethargy (32), or polyphagia (10). For the 50 dogs in which HAC was diagnosed on the basis of results of adrenal function testing, results of a LDDS test were consistent with a diagnosis of HAC in 41, results of an ACTH stimulation test were consistent with a diagnosis of HAC in 5, and results of both tests were consistent with a diagnosis of HAC in 4. For the dog in which HAC was diagnosed on the basis of histologic examination of necropsy specimens, a pituitary microadenoma and bilateral adrenal cortical hyperplasia were seen. For 47 (48%) of the dogs in which adrenal function testing was performed (dogs), results of adrenal function tests were normal. Results of a LDDS test excluded the possibility of HAC in 21 dogs, results of an ACTH stimulation test excluded the possibility of HAC in 21, and results of both tests excluded the possibility of HAC in 5.

For 21 of the 45 (47%) dogs in which results of an LDDS test supported the diagnosis of HAC, the test was performed at least 1 month after insulin treatment for DM had begun. For 17 (38%) dogs, the test was performed within the first month of insulin treatment, and for 4 (9%), the test was performed 1 to 10 months prior to the diagnosis of DM. For the remaining 3 dogs, timing of the LDDS test in relation to diagnosis of DM was not known. For dogs in which a diagnosis of HAC was established after diagnosis of DM, the mean time from initiation of insulin treatment to performance of an LDDS test was 6.4 ± 11.4 months, the median was 2 months, and the range was 0.25 to 60 months.

For 8 of the 9 dogs in which results of an ACTH stimulation test supported the diagnosis of HAC, the test was performed within the first month of insulin treatment for DM. For the other dog, the test was performed 6 months after insulin treatment for DM had begun. Mean time from initiation of insulin treatment to performance of an ACTH stimulation test was 1.2 ± 1.8 months (median, 0.5 month; range, 0.25 to 6 months).

Thirty-one of the 51 (61%) dogs in which HAC was diagnosed were treated with mitotane. Mean duration of mitotane treatment was 13.3 ± 17.3 months (median, 6 months; range, 0.3 to 62 months).
Hypothyroidism was diagnosed in 8 (4%) dogs on the basis of clinical signs and results of a TSH stimulation test (5 dogs), low total T4 and high TSH concentrations (2), or histologic evaluation (1; severe multifocal chronic lymphocytic thyroiditis with follicular atrophy and fibrosis and severe cardiac atherosclerosis). Three other dogs with lower-than-normal total T4 concentrations were not considered to be hypothyroid, because additional testing of thyroid gland function had not been done. Twenty-seven additional dogs had normal total T4 concentration, 10 had normal TSH concentration, and 3 had normal TSH stimulation test results.

Acute pancreatitis was diagnosed in 28 (13%) dogs on the basis of clinical signs and appropriate ultrasonographic or histologic findings. Twenty-three dogs were lethargic, 22 were vomiting, 22 had a poor appetite or anorexia, and 7 had diarrhea. Ultrasonographic findings were consistent with a diagnosis of acute pancreatitis in 27 dogs, and 5 had histologic evidence of acute pancreatitis. In 4 of these dogs, ultrasonographic and histologic findings were suggestive of acute pancreatitis.

Eleven (5%) dogs had tumors for which a histologic diagnosis had been obtained. These included mammary adenocarcinoma and complex mammary adenoma, complex mammary adenoma, mast cell tumor and chronic lymphocytic leukemia, pulmonary carcinoma and lymphosarcoma, hepatic carcinoma, prostatic carcinoma, malignant fibrous histiocytoma of the lung, malignant histiocytosis in the area of the neck, pulmonary carcinoma, ulcerative infiltrative trichoepithelioma, and melanoma.

Abdominal radiography was performed on 46 dogs. Results were normal for 7 dogs and abnormal for 39 (18%). Radiographic abnormalities included hepatomegaly (27 dogs), poor abdominal detail (10), cystic calculi (4), gastric dilation (3), renal mineralization (3), and splenomegaly (2 dogs). Six of the 10 dogs with poor abdominal detail were believed to have acute pancreatitis on the basis of results of abdominal ultrasonography or necropsy.

Thoracic radiography was performed on 100 dogs. Results were normal in 59 dogs and abnormal in 41 (18%). Abnormalities included pulmonary alveolar pattern (15 dogs), cardiomegaly (9), pulmonary interstitial pattern (5), pulmonary nodule (4), pleural effusion (4), pulmonary edema (2), and bronchietasis (2).

Abdominal ultrasonography was performed in 127 dogs. Results were normal in 3 dogs and abnormal in 124 (36%). Abnormalities included hyperechoic liver (104 dogs), hyperechoic renal cortices (48), and hyperechoic pancreas with hyperechoic mesentery consistent with a diagnosis of acute pancreatitis (27). Twenty-three dogs had peritoneal effusion, and 11 had duodenal wall thickening; most of these dogs (19 and 11, respectively) also had ultrasonographic changes consistent with a diagnosis of acute pancreatitis. Splenic ultrasonographic abnormalities were identified in 16 dogs and included hyperechoic spleen (11 dogs), splenic nodules (8), mottled spleen (4), and large splenic masses (2). Twelve dogs had 14 masses that were characterized ultrasonographically, including 6 adrenal gland masses, 2 splenic masses, 2 mammary masses, a thoracic body wall mass, an abdominal body wall mass, a soft tissue mass in the right mid abdomen possibly associated with the small intestine, and a midabdominal mesenteric or intestinal mass. Additional ultrasonographic findings included pyelectasia (14 dogs), cystic calculi (12), hyperechoic liver nodules (12), abdominal (mesenteric, iliac, hepatic, lumbar) lymph node enlargement (11), stomach wall thickening (9), hyperechoic abdominal lymph nodes (8), decreased renal corticomedullary junction distinction (3), hyperechoic liver nodules (4), gall bladder wall thickening (4), renal cysts (3), renal calculi (3), symmetrical hyperechoic enlargement of the prostate (3), prostatic cysts (3), liver cysts (2), distended gall bladder (2), and thickened small intestine (other than duodenum, 2).

A necropsy was performed on 20 (9%) dogs. Mean time from diagnosis of DM to necropsy was 275 ± 320 days (median, 40 days; range, 1 to 2,250 days). The most common gross and histologic necropsy findings was fatty hepatic changes, which were observed in 14 dogs. Eleven of the 14 dogs with histologic evidence of fatty hepatic changes also had hepatomegaly detected on physical examination. Other gross and histologic necropsy findings included subacute or acute necrotizing pancreatitis (5 dogs), age-associated pancreatic lesions (nodular hyperplasia in 1 dog and interstitial fibrosis in another), chronic fibrosing pancreatitis (1), severe lymphoplasmacytic interstitial nephritis (2), interstitial pneumonia (2), chronic pulmonary artery thrombosis (2), chronic severe pyelonephritis (1), pituitary microadenoma (1), and multifocal chronophobe hyperplasia of the pituitary gland (1). Additional findings included bilateral adrenocortical hyperplasia consistent with a diagnosis of HAC (1 dog), adrenocortical adenoma (believed to be nonfunctional because of a lack of cortical atrophy, 1), severe chronic lymphocytic thyroiditis with follicular atrophy and fibrosis and severe cardiac atherosclerosis (1), multiple myocardial infarcts (1), moderate hepatic cirrhosis (1), massive abdominal effusion secondary to hepatic biliary cyst rupture (1), intestinal impaction (1), bilateral otitis media (1), malignant fibrous histiocytoma of the lung (1), mast cell tumor involving several lymph nodes and accompanied by severe transmural gastric hemorrhage and necrosis (1), suppurative prostatitis (1 dog), and severe diffuse cerebellar pseudolaminar necrosis and bilateral thalamic and hypothalamic necrosis (believed to be the result of hypoglycemia) accompanied by severe focal acute hemorrhage and infarct in the mesencephalon (1). In 4 dogs, specific histologic abnormalities were not detected.

**Discussion**

To our knowledge, the present report represents the largest detailed clinical study of dogs with naturally occurring DM in the veterinary literature. Clinical signs, physical examination findings, and CBC results for these dogs were similar to those previously reported for dogs with DM. The most frequently identified serum biochemical abnormalities were high hepatic enzyme activities, lipemia, hypochloremia, and...
hypocalcemia. High hepatic enzyme activities are common in diabetic dogs and may be a result of hepatic lipodosis. Lipemia has also been documented and may be due to lack of activation of lipoprotein lipase by insulin. Hypochloremia may have developed as a result of vomiting; 89 (40%) dogs in the present study were reported to have been vomiting.

Ionized calcium concentration was low in 41 of the 87 (47%) dogs in which it was measured. Abnormal calcium homeostasis is a common metabolic abnormality in diabetic humans and is thought to contribute to many diabetic complications, including altered carbohydrate metabolism, microangiopathy, atherosclerosis, cataract formation, renal disease, and osteopenia. Abnormal calcium homeostasis is also thought to affect insulin secretion and action. The most commonly reported calcium homeostasis abnormality in human diabetics is increased intracellular calcium concentration. However, serum calcium concentration is also often low in humans with insulin-dependent DM. Most diabetic dogs are believed to have insulin-dependent DM and, similar to humans with insulin-dependent DM, typically have a low serum calcium concentration. Further studies are needed to determine the clinical importance of this finding in dogs with DM.

Twenty-eight (13%) dogs in the present study had proteinuria without hemoglobinuria, and bacterial culture of a urine sample did not yield any growth. Proteinuria has been documented in up to 20% of dogs with DM and is thought to be associated with hypertension. However, a cause-and-effect relationship has not been proven. Although 56 dogs in the present study had a venous pH < 7.35, only 34 of these dogs had ketonuria, allowing for a diagnosis of DKA. Some of the dogs with a venous pH < 7.35 may have had ketonuria that was not identified by the nitroprusside reagent on the urine dipstick, which detects mainly acetoacetate. Other dogs may have developed acidemia because of other diseases (such as renal disease), and acidosis was not a result of formation of excess ketones.

We did not attempt to determine the most common concurrent disorders in dogs with DKA versus dogs with uncomplicated DM, because dogs with DKA may have undergone more extensive diagnostic testing to identify concurrent disorders. Thus, the number of concurrent disorders in dogs with DKA may have been artificially increased, compared with the number in dogs with uncomplicated DM. Additionally, some dogs with DKA may have been misclassified as having uncomplicated DM, because ketonuria was not identified by the urine dipstick test.

Coagulation abnormalities were reviewed in the present study, because such disorders may affect the treatment and prognosis of dogs with DM, and because coagulation abnormalities such as increased platelet aggregation and thrombosis have been reported for diabetic humans. Twenty-one (9.5%) dogs were found to have coagulation abnormalities. However, many of these dogs could have had other diseases contributing to coagulation abnormalities, and further studies are required to better define coagulation parameters in dogs with DM.

The most frequently observed concurrent disorders among dogs in the present study were HAC, urinary tract infection, dermatitis, otitis, acute pancreatitis, neoplasia, and hypothyroidism. Therefore, diabetic dogs with insulin resistance or DKA that have clinical signs suggestive of 1 of these disorders should undergo additional diagnostic testing.

The diagnosis of HAC in dogs with DM can be challenging, because clinical signs and clinicopathologic abnormalities associated with these diseases are similar. For example, polyuria, polydipsia, and polyphagia may be a result of either DM or HAC, as can high ALT, AST, and ALP activities. Therefore, at the time of the initial diagnosis of DM, most dogs are not tested for HAC, and clinical signs and clinicopathologic abnormalities are attributed to DM alone.

The diagnosis of HAC in diabetic dogs is further complicated by the fact that results of adrenal function test may be falsely positive in dogs with nonadrenal gland diseases. However, adrenal function test results have been shown to be normal in well-regulated colony dogs with naturally occurring DM and in 47 (48%) dogs in the present study. Most of the dogs in the present study in which HAC was diagnosed were treated with mitotane for prolonged periods. The prolonged treatment of these dogs with mitotane suggests that the diagnosis of HAC was correct.

One of this study’s limitations is that the LDDS test was used for the diagnosis of HAC in most dogs. The LDDS test has been shown to have a specificity as low as 70%, with a false-positive rate of 30%. In the present study, HAC was diagnosed in 41 dogs on the basis of results of an LDDS test. If results for 30% of these 41 dogs were falsely positive, 12 dogs would have been misclassified and did not actually have HAC, decreasing the total number of dogs with HAC in this study from 51 (23%) to 39 (18%). The goal of the present study, however, was not to determine specific percentages of diabetic dogs with each particular concurrent disorder. Rather, we were more interested in identifying the most frequently encountered concurrent disorders in diabetic dogs, and even if several dogs had been misclassified as having HAC when they did not, it is still possible to conclude that HAC is a frequently encountered concurrent disorder in dogs with DM. Therefore, it is recommended that all diabetic dogs in which clinical signs consistent with HAC do not resolve with appropriate insulin treatment be tested for HAC. Additionally, diabetic dogs with insulin resistance or DKA should also be tested for HAC.

Urine samples from 159 dogs in the present study were submitted for aerobic bacterial culture, and results were indicative of urinary tract infection in 34. Infection is 1 of the most common documented causes of ketoacidosis in diabetic humans, and bacterial urinary tract infection in particular is a frequent complication of DM in people. One of the causes of the high incidence of urinary tract infections in humans with poorly controlled DM is thought to be impaired leukocyte function. Decreased intracellular leukocyte bactericidal activity as well as diminished leukocyte phagocytosis, chemotaxis, and adherence have been documented in
humans with poorly controlled DM. Similarly, decreased neutrophil adherence has been demonstrated in dogs with poorly controlled DM. These abnormalities are resolved or significantly reduced in human and canine patients with well-regulated DM. Because urinary tract infection is a common concurrent disorder in dogs with DM, aerobic bacterial culture of a urine sample is recommended for all diabetic dogs that have insulin resistance or DKA.

Decreased neutrophil function may also contribute to development of dermatitis or otitis in dogs with DM. Severe dermatitis and otitis may contribute to increased secretion of counter-regulatory hormones (eg, glucagon, catecholamines, glucocorticoids, and growth hormone), which may result in insulin resistance or DKA. Therefore, these conditions should be treated promptly in dogs with DM.

Acute pancreatitis was diagnosed in 28 (13%) dogs in the present study, and DM has been shown to be a risk factor for acute pancreatitis in dogs. The mechanism by which DM predisposes dogs to develop acute pancreatitis is not known. However, it is possible that hypertriglyceridemia associated with DM may play a role. Hypertriglyceridemia is a risk factor for acute pancreatitis in humans and has been associated experimentally with induction of acute pancreatitis in dogs.

Hypothyroidism was diagnosed in 8 (4%) dogs. Hypothyroidism and insulin-dependent DM are thought to have an underlying immune-mediated cause. Antithyroglobulin antibodies have been demonstrated in dogs with hypothyroidism, and pancreatic beta-cell antibodies have been documented in dogs with DM. It is possible that an underlying immune-mediated process predisposes dogs to both disorders.

Masses were observed in many dogs in the present study, but a histologic diagnosis was obtained for 11. Seven additional dogs were suspected clinically to have neoplastic disease; however, this suspicion was not confirmed by means of histologic evaluation of biopsy or necropsy specimens. The common presence of neoplastic disease in diabetic dogs is probably a result of the fact that DM develops most often in middle-age or older dogs. Clinical signs associated with neoplastic disease; however, this suspicion was not confirmed by means of histologic evaluation of biopsy or necropsy specimens. The common presence of neoplastic disease in diabetic dogs is probably a result of the fact that DM develops most often in middle-age or older dogs. Clinical signs associated with neoplastic disease depend on the organ affected and the extent of tumor spread. Therefore, it is not possible to recommend screening all diabetic dogs for neoplasia. However, the possibility of neoplastic disease should be investigated in dogs with insulin resistance or DKA, because neoplastic disease may result in increased secretion of counter-regulatory hormones that may complicate regulation of DM.

The most common abdominal radiographic abnormality in the present study was hepatomegaly, and the most common abdominal ultrasonographic abnormality was a hyperechoic liver. Additionally, most dogs had evidence of hepatomegaly on physical examination. The most consistent histologic finding in dogs that underwent a necropsy was fatty hepatic changes, and it is likely that hepatomegaly and hyperechoic liver were a result of fatty hepatic changes. In most dogs, results of thoracic radiography were normal, and other diagnostic imaging findings were too varied for conclusions to be made.

Another important limitation of the present study was that only dogs referred to a tertiary care center were included. It is possible that diabetic dogs at tertiary care centers represent a population of dogs with more concurrent disorders than other diabetic dogs. However, the goal of this study was not to investigate the true incidence of concurrent disorders in dogs with DM but rather to identify the most common concurrent disorders. Determining the true incidence of concurrent disorders in dogs with DM would require including diabetic dogs treated by primary care providers. Additionally, all dogs would have to undergo diagnostic testing to confirm whether they did or did not have each disease, which cannot be justified in a clinical setting.

References


