Remission of diabetes mellitus in cats with diabetic ketoacidosis


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Abstract

BACKGROUND: Diabetic ketoacidosis (DKA) has long been considered a key clinical feature of type-1 diabetes mellitus (DM) in humans although. An increasing number of cases of ketoacidosis have been reported in people with type-2 DM. HYPOTHESIS/OBJECTIVES: Cats initially diagnosed with DKA can achieve remission from diabetes. Cats with DKA and diabetic remission are more likely to have been administered glucocorticoids before diagnosis. ANIMALS: Twelve cats with DKA and 7 cats with uncomplicated DM. METHODS: Retrospective case review. Medical records of cats presenting with DKA or DM were evaluated. Diabetic remission was defined as being clinically unremarkable for at least 1 month after insulin withdrawal. The cats were assigned to 1 of 3 groups: (1) cats with DKA and diabetic remission; (2) cats with DKA without diabetic remission; and (3) cats with DM and diabetic remission. RESULTS: Seven cats with DKA had remission from diabetes. These cats had significantly higher concentrations of leukocytes and segmented neutrophils, and significantly lower concentrations of eosinophils in blood and had pancreatic disease more often than did cats with uncomplicated DM and diabetic remission. With regard to pretreatment, 3/7 cats in group 1, 1/5 cats in group 2, and 1/7 cats in group 3 had been treated with glucocorticoids. CONCLUSIONS AND CLINICAL IMPORTANCE: Remission of DM in cats presenting with DKA is possible. Cats with DKA and remission have more components of a stress leucogram, pancreatic disease, and seemed to be treated more often with glucocorticoids than cats with uncomplicated DM and diabetic remission.
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Results: Seven cats with DKA had remission from diabetes. These cats had significantly higher concentrations of leukocytes and segmented neutrophils, and significantly lower concentrations of eosinophils in blood and had pancreatic disease more often than did cats with uncomplicated DM and diabetic remission. With regard to pretreatment, 3/7 cats in group 1, 1/5 cats in group 2, and 1/7 cats in group 3 had been treated with glucocorticoids.

Conclusions and Clinical Importance: Remission of DM in cats presenting with DKA is possible. Cats with DKA and remission have more components of a stress leukogram, pancreatic disease, and seemed to be treated more often with glucocorticoids than cats with uncomplicated DM and diabetic remission.

Key words: Cats; Diabetic ketoacidosis; Remission of disease.

Diabetes mellitus (DM) is one of the most frequently encountered endocrine disorders in cats. The current classification scheme adapted from human medicine differentiates among type-1 DM, provoked by immune-mediated destruction of β-cells, type-2 DM characterized by inadequate insulin secretion and impaired insulin action, and other specific types of DM induced by medical conditions causing insulin resistance or destruction of pancreatic tissue.1 The spontaneous form of DM in cats seems very similar to type-2 DM in humans; obesity is strongly correlated with insulin resistance and remission of disease can often be achieved with insulin therapy.2–7

Diabetic ketoacidosis (DKA) is the most serious hyperglycemic emergency in patients with DM.

The basic underlying mechanism is a reduction in the net effective action of circulating insulin coupled with increased levels of counterregulatory hormones.8,9 Underlying clinical disorders (eg, systemic infection), therapy with diabetogenic medications (eg, glucocorticoids), or omission and underdosage of insulin are often precipitating events.10 In human medicine, DKA has long been considered a key clinical feature of type-1 DM. Recently, however, it has been demonstrated that ketoacidosis also occurs in subjects with type-2 DM.11–14

Today, human patients who develop ketoacidosis are reported as suffering from ketosis-prone diabetes (KPD) and are classified into 4 different groups: (1) KPD type-1A—individuals with permanent and complete β-cell failure with serologic markers of islet cell autoimmunity who require lifelong insulin therapy; (2) KPD type-1B—individuals with permanent and complete β-cell failure but lack of serologic markers of islet cell autoimmunity who require lifelong insulin therapy; (3) KPD type-2A—individuals with present β-cell function and with serologic markers of islet cell autoimmunity. Some experience progressive disease requiring lifelong insulin therapy, in others insulin therapy can be discontinued; and (4) KPD type-2B—individuals with preserved β-cell function and lack of serologic markers of islet cell autoimmunity.14

Typically, these latter subjects are obese, middle-aged, and have a strong family history of type-2 DM.15 At presentation, they have impairment of both insulin secretion and insulin action and are therefore insulin dependent, but aggressive management results in significant improvement in β-cell function and insulin sensitivity followed by absence of insulin requirement for months to years.13,16

In veterinary medicine, diabetic remission has been reported in up to 50% of cats with DM.6,7 One report mentions 5 stable diabetic cats with trace ketonuria which had remission from diabetes.5 To the best of our knowledge, however, diabetic remission in severely deteriorated ketoacidotic cats has not been reported. Because the spontaneous form of feline DM closely resembles the human type-2 DM, a similar course as in some human patients with KPD type-2B, could easily be figured. The purpose of this study was, therefore, to evaluate medical records of cats presenting with DKA with diabetic remission and to compare them with those of cats with DKA without diabetic remission and those of cats with uncomplicated DM and diabetic remission.
Materials and Methods

Inclusion Criteria

Medical records of cats with DM or DKA presented between February 2003 and July 2007 to the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Switzerland were reviewed retrospectively. DM was diagnosed based on clinical signs, hyperglycemia (> 162 mg/dL), glucosuria, and increased fructosamine concentrations (> 340 µmol/L). DKA was defined by the presence of typical clinical signs, ketonuria, and metabolic acidosis (either pH < 7.3 or TCO2 < 15 mmol/L). Only cats with newly diagnosed DM or DKA in which results of CBC, serum biochemistry, urinalysis, urine protein-to-creatinine ratio, and abdominal ultrasonography from the initial presentation were available, in which owners were willing to treat and which survived the initial stabilization period were included.

Treatment and Reevaluations

Cats with uncomplicated DM were treated with intermediate-acting insulin (porcine lente insulin$^4$ [n = 5] or glargine$^2$ [n = 2], starting dose 0.25–0.5 U/kg q12h) and a commercial high-protein, low-carbohydrate diet (Hill’s Science Plan, Feline Growth$^7$ [n = 2], DM Purina$^4$ [n = 5]).

Cats with DKA were treated with a standardized DKA protocol. This protocol included: infusion therapy with 0.9% NaCl; supplementation of potassium and phosphorus; monitoring and adaptation of electrolyte supplementation every 4–6 hours; IM insulin therapy with short-acting insulin (starting dose 0.05–0.1 U/kg/h); amoxicillin–clavulanic acid (12.5 mg/kg q12h); buprenorphine (0.03 mL/kg q8h); low molecular weight heparin (100 U/kg q24h); and other treatments (eg, metoclopramide, tiethylperazin, ursodeoxycholic acid, nutritional support) as needed. Once ketonuria had resolved and cats were eating and drinking, insulin therapy was changed to intermediate-acting insulin (porcine lente insulin$^4$ starting dose 0.25–0.5 U/kg q12h). At the time of discharge a commercial high-protein, low-carbohydrate diet was prescribed (Hill’s Science Plan Feline Growth$^7$ [n = 8], DM Purina$^4$ [n = 4]).

Reevaluations included an updated history, physical examination, measurement of total protein, albumin and fructosamine concentrations, and a 12-hour blood glucose curve. Insulin therapy was adjusted based on the glucose nadir: when the nadir was <90, 90–162, or ≥162 mg/dL, the insulin dose was decreased (0.5–1 U/cat), left unchanged, or increased (0.5–1 U/cat), respectively.

Diabetic Remission

Diabetic remission was defined as being clinically unremarkable, having normalized blood glucose and fructosamine concentrations and needing no more insulin for at least 1 month after treatment cessation.

Diagnosis of Concurrent Diseases

Routine abdominal ultrasound including evaluation of the pancreas was performed with a 5–8 MHz curved array transducer.$^7$ Echogenicity, texture, and contour of the pancreas were evaluated. The thicknesses of the right and left pancreatic lobes and major duodenal papilla, as well as the width of the right and left pancreatic ducts were measured. Free abdominal fluid, hyperechoic mesentry, lymphadenomegaly, or other abdominal diseases were also recorded. The normal feline pancreas was defined as hypo- to isoechoic in comparison with the liver, with an uniform architecture, regular contours, and normal dimensions.$^{17}$ Ultrasonographic evidence of pancreatic disease included diffuse hypoechochogenicity, hyperechochogenicity or heterogeneity, enlargement, irregular borders, nodules, masses, pseudocysts or abcesses, and concomitant findings such as hyperechoic mesentery, focal abdominal effusion, lymph node enlargement, corrugation of the duodenum, and signs of extrapancreatic biliary obstruction.$^{17}$ Because ultrasonographic findings overlap for different pancreatic diseases, a definitive diagnosis was not possible. The final radiologic assessment, therefore, consisted of either acute or chronic pancreatic disease. In 2 cats ultrasound-guided fine needle aspirates of the altered pancreas were taken. In both, not enough cellular material was available for a definite diagnosis.

Urinary tract infection was diagnosed by a positive bacteriologic culture of urine samples obtained by means of antepubic cystocentesis.

Hypertrophic cardiomyopathy was diagnosed based on typical echocardiographic findings.

Groups of Cats

Cats were assigned to the following 3 groups: (1) cats with DKA and diabetic remission; (2) cats with DKA without diabetic remission; and (3) cats with uncomplicated DM and diabetic remission.

Statistical Analyses

Results were analyzed by use of nonparametric statistical methods.$^5$ Ranges and median values are reported. Differences among the groups were tested by use of the Mann-Whitney U-test. The Fisher’s exact test was used to test differences between concurrent diseases and pretreatments. The level of significance was set at $P < .05$.

Results

Cats with DKA

During the study period 24 cats with DKA were presented. Twelve cats fulfilled the inclusion criteria and were finally enrolled.

Seven cats had remission from diabetes (group 1). Age ranged from 2 to 14 years (median, 12 years) and bodyweight from 5.0 to 6.5 kg (median, 5.5 kg). One was female spayed and 6 were male castrated. Breeds included 4 domestic shorthair cats, 1 Siamese, 1 Burmese, and 1 Maine Coon cat.

Five cats with DKA did not experience diabetic remission (group 2). Age ranged from 7 to 14 years (median, 11 years) and bodyweight from 3.7 to 7.8 kg (median, 4.5 kg). Two were female spayed and 3 male castrated. Breeds included 3 domestic shorthair cats, 1 British Shorthair Blue, and 1 British Shorthair Blue Mixed cat.

Cats with Uncomplicated DM

During the study period 52 cats with uncomplicated DM were presented. Seven cats fulfilled the inclusion criteria and were finally enrolled (group 3). Age ranged from 7 to 17 years (median, 12 years) and bodyweight from 3.0 to 10 kg (median, 5.7 kg). Four were female spayed and 3 male castrated. All were domestic shorthair cats.
Duration of Clinical Signs before Presentation

Duration of clinical signs before presentation ranged from 2 to 4 weeks (median, 3 weeks) in group 1, from 2 to 8 weeks (median, 4 weeks) in group 2, and from 2 to 12 weeks (median, 4 weeks) in group 3. There was no significant difference in duration of clinical signs before presentation among the groups.

Signalment and Laboratory Results (Tables 1 and 2)

There was no significant difference in age, sex, or bodyweight among the 3 groups; however, bodyweight in group 1 was much less variable than that of the 2 other groups (Fig 1).

All significant differences in laboratory results among the 3 groups are listed in Tables 1 and 2. Following, only the clinical important differences are mentioned.

Cats of group 1 had significantly higher leukocytes and segmented neutrophils and significantly lower eosinophils than cats of group 3.

Cats of groups 1 and 2 (cats with DKA) had lower serum blood glucose concentrations than cats of group 3, although the difference was only significant between cats of groups 1 and 3.

Cats of groups 1 and 2 (cats with DKA) had significantly higher bilirubin, aspartate aminotransferase, and alanine aminotransferase levels, significantly lower potassium and calcium concentrations and significantly higher urine ketone bodies, and urine protein-to-urine-creatinine ratios than cats of group 3.

Concurrent Diseases

Suspected concurrent diseases included: pancreatic disease (n = 7; 5 in group 1 and 2 in group 2), bacterial cystitis (n = 4; 1 in group 1, 2 in group 2, and 1 in group 3), and hypertrophic cardiomyopathy (n = 1; 1 in group 2).

Cats of group 1 suffered significantly more often from pancreatic disease than cats of group 3.

Liver disease was excluded from the list of concurrent diseases. Definitive differentiation between primary hepatic disease and changes secondary to DM or pancreatitis seemed impossible without either cytologic or histologic liver examination in each cat.

Pretreatments

Five cats had been pretreated with glucocorticoids by private veterinarians before the development of DKA.

Three cats of group 1: 2 for chronic skin problems (1 with SC methylprednisolone 1/2 year ago and PO prednisolone over 2 weeks, 3 weeks before presentation; 1 with SC dexamethasone, twice, 6 months apart, the last time 2 weeks before presentation), and 1 for chronic vomiting (with SC flumethasone, 3–4 times, every 4–6 weeks, last time 2 weeks before presentation).

One cat of group 2; for a reoccurring mast cell tumor (with PO prednisolone over 6–8 weeks, 2 and 3 years ago, ocular dexamethasone over 6–8 weeks, 2 and 3 years ago, and a local-acting intralesional glucocorticoid, 6 times over the last 3 years, last time 3 weeks before presentation).

One cat of group 3; for a chronic respiratory disease (with SC flumethasone, every 1/2 year over 2 years, last time 4 weeks before presentation).

Statistically, the number of pretreated cats was not significantly different among the 3 groups.

Outcome

Group 1

Median time of hospitalization for cats in group 1 was 9 days (5–16 days).

Table 1. Hematologic parameters in cats with DKA and diabetic remission, cats with DKA without diabetic remission, and cats with DM and diabetic remission.

<table>
<thead>
<tr>
<th>Blood Parameters</th>
<th>Group 1 (n = 7)</th>
<th>Group 2 (n = 5)</th>
<th>Group 3 (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>%</td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>36 (23–40)</td>
<td>38 (31–41)</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>10^6/μL</td>
<td>8.2 (5.86–10.6)</td>
<td>8.7 (6.0–10.2)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>10^3/μL</td>
<td>17.8 (10.4–36.8)a</td>
<td>10.1 (9.4–26.8)</td>
</tr>
<tr>
<td>MCV</td>
<td>fl</td>
<td>40 (38–44)</td>
<td>45 (39–52)</td>
</tr>
<tr>
<td>MCHC</td>
<td>g/dL</td>
<td>35 (31–36)</td>
<td>33 (32–35)</td>
</tr>
<tr>
<td>Platelets</td>
<td>10^3/μL</td>
<td>222 (130–325)</td>
<td>380 (200–380)</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>/μL</td>
<td>17090 (9360–32940)a</td>
<td>7676 (6100–35870)</td>
</tr>
<tr>
<td>Nonsegmented neutrophils</td>
<td>/μL</td>
<td>40 (0–1930)</td>
<td>0 (0–340)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>/μL</td>
<td>140 (0–520)a</td>
<td>303 (0–810)</td>
</tr>
<tr>
<td>Basophils</td>
<td>/μL</td>
<td>50 (0–180)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>/μL</td>
<td>410 (50–8000)</td>
<td>300 (140–660)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>/μL</td>
<td>755 (310–1240)</td>
<td>1270 (210–3170)</td>
</tr>
</tbody>
</table>

*P < .05 versus group 3.

DKA, diabetic ketoacidosis; DM, diabetes mellitus; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration.
Three of the 7 cats are still alive and in diabetic remission at the time of writing. Insulin was withdrawn after 10 days, 2, or 4 weeks. Up till now, remission lasted for 24, 16, and 10 months, respectively.

Four of the 7 cats came out of remission. Insulin was withdrawn after 1 (n = 5), 4, and 5 weeks. Remission lasted for 5 and 6 months, 5 weeks and 4 months, respectively. All cats were euthanized after 2 or 2.5 (n = 3) years. Reasons for euthanasia were known in 3 cats, being decompensated chronic renal failure, intestinal lymphoma, and brain tumor. One cat was euthanized because of geriatric reasons.

### Table 2. Biochemical parameters in cats with DKA and diabetic remission, cats with DKA without diabetic remission, and cats with DM and diabetic remission.

<table>
<thead>
<tr>
<th>Blood Parameters</th>
<th>Unit</th>
<th>Group 1 (DKA, remission)</th>
<th>Median</th>
<th>Range</th>
<th>Group 2 (DKA, no remission)</th>
<th>Median</th>
<th>Range</th>
<th>Group 3 (non-DKA diabetics, remission)</th>
<th>Median</th>
<th>Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>mg/dL</td>
<td></td>
<td>2.0</td>
<td>(0.2–4.1)</td>
<td>0.9</td>
<td>(0.2–1.8)</td>
<td>0.15</td>
<td>(0.06–0.3)</td>
<td>0.1–0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td></td>
<td>259</td>
<td>(175–450)</td>
<td>394</td>
<td>(281–571)</td>
<td>504</td>
<td>(322–659)</td>
<td>72–162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructosamine</td>
<td>μmol/L</td>
<td></td>
<td>623</td>
<td>(487–742)</td>
<td>670</td>
<td>(500–709)</td>
<td>685</td>
<td>(526–768)</td>
<td>&lt;340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>mg/dL</td>
<td></td>
<td>20</td>
<td>(17–66)</td>
<td>21.5</td>
<td>(17.4–25.5)</td>
<td>26</td>
<td>(12.6–47.6)</td>
<td>20.7–35.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td></td>
<td>1.1</td>
<td>(0.7–2.7)</td>
<td>1.2</td>
<td>(0.9–1.4)</td>
<td>1.14</td>
<td>(0.7–1.4)</td>
<td>1.1–1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, total</td>
<td>g/dL</td>
<td></td>
<td>7.1</td>
<td>(5.1–8.6)</td>
<td>7.4</td>
<td>(6.4–8.0)</td>
<td>7.2</td>
<td>(7.1–7.9)</td>
<td>6.4–8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>g/dL</td>
<td></td>
<td>3.6</td>
<td>(2.2–4.1)</td>
<td>3.6</td>
<td>(3.1–3.7)</td>
<td>3.6</td>
<td>(2.9–3.9)</td>
<td>3.0–4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>mg/dL</td>
<td></td>
<td>259</td>
<td>(259–469)</td>
<td>333</td>
<td>(166–468)</td>
<td>232</td>
<td>(166–337)</td>
<td>101–263</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>U/L</td>
<td></td>
<td>44</td>
<td>(16–83)</td>
<td>56</td>
<td>(23–101)</td>
<td>59</td>
<td>(36–83)</td>
<td>16–43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAT</td>
<td>U/L</td>
<td></td>
<td>173</td>
<td>(109–386)</td>
<td>207</td>
<td>(30–502)</td>
<td>29</td>
<td>(20–88)</td>
<td>19–44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALAT</td>
<td>U/L</td>
<td></td>
<td>198</td>
<td>(141–584)</td>
<td>244</td>
<td>(69–444)</td>
<td>61</td>
<td>(43–190)</td>
<td>34–98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>U/L</td>
<td></td>
<td>36</td>
<td>(20–415)</td>
<td>44</td>
<td>(10–113)</td>
<td>21</td>
<td>(10–37)</td>
<td>8–26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>mEq/L</td>
<td></td>
<td>156</td>
<td>(140–163)</td>
<td>161</td>
<td>(158–163)</td>
<td>160</td>
<td>(155–163)</td>
<td>158–165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>mEq/L</td>
<td></td>
<td>3.4</td>
<td>(2.1–5.4)</td>
<td>4.1</td>
<td>(3.3–4.9)</td>
<td>5.0</td>
<td>(4.7–5.8)</td>
<td>3.8–5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>mEq/L</td>
<td></td>
<td>105</td>
<td>(91–113)</td>
<td>112</td>
<td>(108–120)</td>
<td>113</td>
<td>(110–119)</td>
<td>121–131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/dL</td>
<td></td>
<td>8.4</td>
<td>(6.0–10.4)</td>
<td>9.3</td>
<td>(9.0–10.6)</td>
<td>10.6</td>
<td>(9.8–11.4)</td>
<td>9.6–11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>mg/dL</td>
<td></td>
<td>3.2</td>
<td>(0.7–4.7)</td>
<td>3.26</td>
<td>(1.46–4.43)</td>
<td>4.3</td>
<td>(3.2–4.7)</td>
<td>2.8–5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td>7.2</td>
<td>(7.1–7.3)</td>
<td>7.1</td>
<td>(7.0–7.3)</td>
<td>ND</td>
<td>ND</td>
<td>7.28–7.41</td>
<td></td>
<td></td>
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<tr>
<td>PCO₂</td>
<td>mmHg</td>
<td></td>
<td>35.5</td>
<td>(25.8–37.4)</td>
<td>37.2</td>
<td>(35.5–45.7)</td>
<td>ND</td>
<td>ND</td>
<td>33–45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCO₃</td>
<td>mEq/L</td>
<td></td>
<td>13.9</td>
<td>(10.5–16.5)</td>
<td>12.8</td>
<td>(9.0–18.4)</td>
<td>ND</td>
<td>ND</td>
<td>18–23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TotCO₂</td>
<td>mEq/L</td>
<td></td>
<td>13.9</td>
<td>(9.0–17.5)</td>
<td>14.0</td>
<td>(9.6–20.1)</td>
<td>ND</td>
<td>ND</td>
<td>12.5–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap</td>
<td>mEq/L</td>
<td></td>
<td>38.2</td>
<td>(25.7–47)</td>
<td>37.8</td>
<td>(31.3–44.1)</td>
<td>ND</td>
<td>ND</td>
<td>13–27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>mEq/L</td>
<td></td>
<td>327</td>
<td>(302–360)</td>
<td>350</td>
<td>(346–361)</td>
<td>358</td>
<td>(339–367)</td>
<td>308–335</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine ketone bodies</td>
<td>n+</td>
<td></td>
<td>4+</td>
<td>(2+–4+)</td>
<td>2+</td>
<td>(1+–4+)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPC</td>
<td></td>
<td></td>
<td>1.4</td>
<td>(0.2–3.0)</td>
<td>1.3</td>
<td>(0.5–8.6)</td>
<td>0.2</td>
<td>(0.1–0.5)</td>
<td>&lt; 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal thyroxin</td>
<td>μg/dL</td>
<td></td>
<td>1.8</td>
<td>(1.1–2.3)</td>
<td>1.2</td>
<td>(0.1–2.2)</td>
<td>1.2</td>
<td>(0.7–1.9)</td>
<td>&lt; 3.5</td>
<td></td>
<td></td>
</tr>
</tbody>
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aP < 0.05 versus group 3.
bP < 0.05 versus group 2.
cP < 0.05 versus group 3.
dCommercially available radioimmunoassay validated for use in cats.

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; DKA, diabetic ketoacidosis; DM, diabetes mellitus; UPC, urine protein-to-creatinine ratio.

Three of the 7 cats are still alive and in diabetic remission at the time of writing. Insulin was withdrawn after 10 days, 2, or 4 weeks. Up till now, remission lasted for 24, 16, and 10 months, respectively.

Four of the 7 cats came out of remission. Insulin was withdrawn after 1 (n = 2), 4, and 5 weeks. Remission lasted for 5 and 6 months, 5 weeks and 4 months, respectively. All cats were euthanized after 2 or 2.5 (n = 3) years. Reasons for euthanasia were known in 3 cats, being decompensated chronic renal failure, intestinal lymphoma, and brain tumor. One cat was euthanized because of geriatric reasons.

### Group 2

Median time of hospitalization for cats in group 2 was 8 days (8–10 days).

In 4 of the 5 cats DM was well controlled. The insulin need ranged from 0.5 to 3 U/cat twice daily. Two cats are still alive at the time of writing 2.5 and 3 years after initial diagnosis. One cat was euthanized after 3.5 years owing to geriatric reasons. One cat developed another episode of DKA 5 months after initial presentation and the owner opted for euthanasia.

In 1 of the 5 cats DM was poorly controlled. During the first 14 weeks insulin was steadily increased to 7 U/cat.

![Fig. 1. Point plots of bodyweight (kg) of the 3 groups of cats. Group 1 (7 cats): cats with diabetic ketoacidosis (DKA) and diabetic remission; group 2 (5 cats): cats with DKA without diabetic remission; group 3 (7 cats): cats with uncomplicated diabetes mellitus and diabetic remission.](image-url)
twice daily. Thereafter, somogy phenomenon was suspected and the insulin dose was decreased to 4 U/cat twice daily. The cat was lost for follow-up after 8 months.

**Group 3**

Three of the 7 cats are still alive and in diabetic remission at the time of writing. Insulin was withdrawn after 2, 10, or 13 weeks. Up till now, remission lasted for 10, 9, and 36 months, respectively. Two cats stayed in remission until euthanasia after 2 and 3 years. Insulin was withdrawn after 20 and 3 weeks and remission lasted for about 19 and 35 months, respectively. The 2 cats were euthanized owing to geriatric reasons or severe weight loss and anorexia of unknown origin.

Two of the 7 cats came out of remission. In 1 cat insulin was stopped after 3 weeks, had to be restarted 6 months later, and had to be stopped again 6 weeks after the second start of therapy. At that time a kitten had been introduced into the household, which resulted in increased activity and weight loss of the diabetic cat. After the second time of insulin cessation the cat never needed insulin again and at the moment of writing is still alive 3 years after the initial diagnosis. The other cat came down with a left-sided vestibular syndrome caused by an otitis media 7.5 months after insulin treatment cessation and got treated by our neurology service with antibiotics and prednisolone. Eight weeks later the cat presented again with clinical signs of DM and had to be restarted on insulin. The cat needed insulin until euthanasia 3 weeks later owing to dyspnea and a pulmonary mass.

**Comparison of Outcome**

Duration of hospitalization was no significantly different between groups 1 or 2. There was no significant difference in the number of cats that stayed in remission or came out of remission between cats of group 1 and cats of group 3.

**Discussion**

With the present study we wanted to investigate if cats with DKA can experience diabetic remission. In line with reports from human medicine and corroborating our first hypothesis, we were able to document that diabetic remission in cats presenting with DKA is possible. Classification of DM in veterinary medicine is not as sophisticated as in human medicine. However, the assumption that cats with DKA and diabetic remission have some preserved β-cells function seems eligible, hence allocation of these cats into either the human KPD type-2A or B group seems correct. Antibodies against β-cells or insulin at the time of diagnosis in untreated diabetic cats have not been detected which leads to the conclusion that diabetes in cats is not caused by an autoimmune process. The cats with DKA and diabetic remission of this study would, therefore, most likely fall into the human KPD type-2B group.

Because obesity is the major risk factor for the development of type-2 DM in humans one would expect patients with KPD type-2 to have higher bodyweights than patients with KPD type-1. Accordingly, the body mass index of patient with type-1 DM and DKA was significantly lower than that of patients with type-2 DM with or without DKA. Interestingly, bodyweight of our cats did not differ significantly among the 3 groups. On 1 hand, this could be because of the low case number. On the other hand, the problem of classifying DM in cats could be the reason. Cats which experience diabetic remission (cats of groups 1 and 3) suffer from type-2 DM. Cats without diabetic remission (cats of group 2), however, could either have a type-1 DM or an irreversible form of type-2 DM. Two of the cats in group 2, had a bodyweight of ≥6.4 kg. One of them had a 2-year history of an eyelid mast cell tumor, which was surgically removed but reoccurred. Supportive to the surgical tumor therapy the cat was treated with different types of glucocorticoids. The other cat never achieved a good diabetic control. The insulin need seemed erratic and an underlying disease causing insulin resistance was suspected. Hence, these 2 cats more likely suffered from irreversible type-2 DM, caused by long-lasting insulin resistance. The other 3 cats of group 2 had much lower bodyweights and possibly really suffered from type-1 DM. Therefore, the group assignment of this study might not coincide with one based on type-1 or type-2 DM. In future, tests like the newly developed immunoradiometric assay or the enzyme-linked immunosorbent assay for feline proinsulin may prove useful to evaluate β-cells function and assess the likelihood of a diabetic cat to go into remission.

DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counterregulatory hormones. These hormonal imbalances enhance hepatic gluconeogenesis, glycogenolysis, and lipolysis. Patients with type-2 DM are rarely completely deficient in circulating insulin and therefore would be expected to be able to avoid excessive lipolysis and ketogenesis.

The predominant mechanism for the development of DKA in type-DM seems the diminished insulin secretion or the β-cell dysfunction. Endogenous insulin secretion, measured by C-peptide levels, was lowest in type-1 ketotic patients, followed by type-2 ketotic patients and highest in type-2 nonketotic patients. Both ketogenic groups had mean C-peptide levels that were significantly different from the nonketotic DM2 group. The cause of severe insulopenia in type-2 DM with DKA remains uncertain but it was shown that patients who achieved normoglycemic remission had an 80% improvement in fasting and stimulated C-peptide levels. This indicates that the diminished insulin secretion cannot be attributed to irreversible β-cell damage but can be attributed to transient functional abnormalities of the β-cell. One cause for a transient dysfunction of β-cells, is β-cell desensitization by increased plasma glucose. After long-term exposure to chronic hyperglycemia irreversible alterations in β-cell function and structure occur, referred to as glucose toxicity. In patients with ketosensitive type-2 DM, ketotic relapses were preceded by a 12-month progressive rise in blood glucose and β-cells function dramatically deteriorated between the onset of hyperglycemia and readmission for relapse. Thus, it
was concluded that patients with ketosis-prone type-2 DM cannot sustain chronic hyperglycaemia without developing severe β-cell failure and that these individuals have a β-cell propensity to glucose toxicity. Owing to the retrospective nature of the study, insulin secretion was not assessed. Susceptibility of cats to glucose desensitization and glucose toxicity has, however, already been proposed by others.5,23

Beside mechanisms that impair β-cell function, precipitating factors leading to decompensation of type-2 DM have to be considered. Worldwide, infection is the most common precipitating cause for DKA. Other reported factors in human patients include cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, and drugs that affect carbohydrate metabolism like corticosteroids. In this study, cats with DKA and diabetic remission revealed more components of a stress leucogram (higher segmented neutrophils and lower eosinophil counts) and significantly more often ultrasonographic signs for pancreatic disease than cats with uncomplicated DM and diabetic remission. The haematologic differences are a hint toward some concurrent, possibly precipitating disease-causing stress. Together with the ultrasonographic changes the most likely concurrent illness and possibly one reason that cats with type-2 DM develop ketoacidosis seems pancreatic disease. Coexisting acute pancreatitis and DKA occurs in at least 10–15% of human patients. In a study of 42 cats with diabetic ketosis and ketoacidosis pancreatitis was 1 of the most prevalent concurrent disorders. The diagnosis of pancreatitis in cats has, however, to be discussed. At the moment there is no single clinical test with which pancreatitis can reliably be diagnosed. Measurement of the feline pancreatic lipase immunoreactivity (fPLI) in combination with abdominal ultrasound seems the most accurate way to get a proper diagnosis. However, the availability of fPLI used to be restricted and the sensitivity of abdominal ultrasound is low to moderate. A variety of ultrasonographic changes have been reported in cats with pancreatitis, including a normal pancreas. For a definitive diagnosis, cytology or even histology is required. Unfortunately, cytologic or histologic diagnoses were not available in the present study. Therefore, only cats with obvious ultrasonographic alterations in the area of the pancreas were called to have pancreatic disease and the occurrence of pancreatic disease could be underestimated. Three of 7 cats with DKA and diabetic remission and 1/7 cats with uncomplicated DM and diabetic remission had been treated with glucocorticoids by their private veterinarian. Although the difference was not statistically significant, glucocorticoid treatment might be a contributing factor for the development of DKA in type-2 DM in cats.

That cats with DKA and diabetic remission are more often pretreated with glucocorticoids than cats with DKA without diabetic remission was our second hypothesis. Results from this study reveal, that cats with DKA and diabetic remission suffered significantly more often from pancreatic disease and possibly tended to be pretreated more often with glucocorticoids than cats with DKA without diabetic remission. An explanation for this finding could be that, if a precipitating factor, like pancreatitis or glucocorticoid treatment can be found and eliminated, the chance of attaining diabetic remission increases.

In conclusion, complete or partial remission of DM in cats presenting with DKA is possible. This finding seems important, because it may influences the willingness of owners to treat their cats for ketoacidosis. Cats with DKA and diabetic remission suffered more often from pancreatic disease, revealed more components of a stress leucogram and seemed to be treated more often with glucocorticoids than cats with uncomplicated DM. Although the underlying pathomechanism why cats with type-2 DM develop DKA has to be evaluated further, this study strongly supports that pancreatic disease and treatment with glucocorticoids are contributing factors. In future, assessment of insulin secretion of cats with type-2 DM and DKA should be performed, to evaluate if severe isulinopenia, as seen in human patients, is also the predominant mechanism for the development of ketoacidosis in these cats.

References


