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Retrospective Study

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Retrospective evaluation of risk factors and outcome predictors in cats with diabetic ketoacidosis (1997–2007): 93 cases

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Abstract

Objectives – To determine risk factors and outcome predictors in cats with diabetic ketoacidosis (DKA).
Design – Retrospective study. Inclusion in the DKA group required blood glucose concentration > 13.9 mmol/L (250 mg/dL), venous pH < 7.35, and urine or serum acetoacetate concentration greater than 1.5 mmol/L (15 mg/dL). Signalment and weight were recorded in all cats with uncomplicated diabetes mellitus (DM) without DKA and in all other nondiabetic cats examined during the study period. Clinicopathologic variables, concurrent disorders, and initial insulin intravenous (IV) continuous-rate infusion (CRI) concentration of 1.1 or 2.2 U/kg/240 mL bag of 0.9% NaCl, were examined for a possible association with outcome.
Setting – University teaching hospital.
Animals – Ninety-three cats with DKA, 682 cats with uncomplicated DM, and 16,926 cats without DM or DKA.
Interventions – None.
Measurements and Main Results – Cats with DKA were younger (median age 9.4 years; range, 1–17.9 years) than cats with uncomplicated DM (median 11.6 years; range 0.7–19.5 years, $P < 0.0003$). Siamese cats were overrepresented in the DKA group compared to the uncomplicated DM or nondiabetic group ($P = 0.038$ and $P = 0.01$, respectively). Poor outcome (defined as death due to disease or by euthanasia) in 36 cats with DKA (39%) was associated with increased initial creatinine, BUN, total serum magnesium, and total bilirubin concentrations ($P = 0.007$, $P = 0.005$, $P = 0.03$, $P = 0.03$, respectively). Cats treated with a higher concentration of insulin were less likely to have a poor outcome compared to cats treated with a lower concentration of insulin (odds ratio 0.14, 95% confidence interval 0.02–1.16, $P = 0.02$).
Conclusions – Cats with DKA are more likely to be Siamese than cats with uncomplicated DM. Poor outcome of cats with DKA is associated with increased initial creatinine, BUN, total magnesium, and total bilirubin concentrations. Good outcome was associated with a higher concentration of IV insulin CRI.

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Keywords: DKA, feline diabetes, metabolic complications, outcome

Abbreviations

CI	confidence interval
CRI	continuous rate infusion
DM	diabetes mellitus
DKA	diabetic ketoacidosis
IV	intravenous
OR	odds ratio
SC	subcutaneous

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Introduction

Diabetic ketoacidosis (DKA) in cats is a form of complicated diabetes mellitus (DM), which requires intensive therapeutic intervention and monitoring. Several retrospective studies describing clinical signs, clinicopathologic findings, and concurrent disorders of cats with DKA have been published, but these previous smaller studies grouped diabetic cats with ketonuria into one study population, whether or not acidemia was documented, limiting the conclusions that can be applied to

cats with DKA.[1–6] While the pathophysiology of DKA in cats is incompletely understood, these studies suggest that presence of concurrent disorders in cats with newly diagnosed DM increases the risk of DKA.[1,2] However, specific risk factors for development of DKA in cats, and outcome predictors for cats with DKA have not been reported. The goals of this study were to investigate whether breed, age, sex, or weight is associated with increased risk for DKA in cats and to identify variables that may predict the outcome of cats with DKA. In order to achieve these goals, a large population of diabetic cats with ketonuria and acidemia was examined, and the signalment and weight of cats with DKA were compared to the signalment and weight of cats with uncomplicated DM and cats with nondiabetic disease. Detailed analyses of potential outcome predictors within the large group of cats with DKA were also performed. It was hypothesized that analysis of variables in a large group of cats with a rigorous definition of DKA, and comparison of some of these variables to those reported in cats with uncomplicated DM or nondiabetic disease may identify risk factors and outcome predictors for cats with DKA.

Materials and Methods

Criteria for selection of cats with diabetic ketoacidosis

A computer search of all cats admitted to the Matthew J. Ryan Veterinary Hospital of The University of Pennsylvania between January 1, 1997 and December 31, 2007 with a coded medical diagnosis of DKA was performed. Medical records were reviewed in detail. Inclusion criteria were presence of clinical signs suggestive of DM (eg, polyuria, polydipsia, polyphagia, or weight loss) and persistent hyperglycemia and glucosuria, or persistent hyperglycemia despite insulin treatment. Hyperglycemia was defined as blood glucose concentration greater than 13.9 mmol/L (250 mg/dL). Blood glucose concentration was determined by at least 1 of 3 different methods during initial evaluation (serum biochemistry screen,[a] point-of-care analyzer,[b] or glucometer[c]). Additional inclusion criteria were a venous pH < 7.35[b] and ketonuria or ketosis, defined as a urine or serum acetoacetate concentration greater than 1.5 mmol/L (15 mg/dL).[7,d]

Criteria for selection of cats with uncomplicated DM or nondiabetic disease

Another computer search of all cats admitted to the same veterinary teaching hospital during the same time period identified all cats with a coded medical diagnosis of DM and without a coded diagnosis of DKA. Inclusion in this group required persistent hyperglycemia with a blood glucose concentration greater than 13.9 mmol/L (250 mg/dL), glucosuria, documented absence of ketonuria, and a venous pH ≥7.35.[b] This group of cats was used as a signalment and weight comparison group that had uncomplicated DM. Cats in which these inclusion criteria were met and a diagnosis of DM was confirmed were included in this group whether or not they had received prior insulin treatment.

All cats that were examined at the hospital during the same time period without a diagnosis of DM or DKA were used as a nondiabetic signalment and weight comparison population. The nondiabetic signalment comparison group included cats examined for preventative health care and routine wellness visits. The DM and nondiabetic comparison groups were used for the purpose of signalment and weight comparisons only. No other data were analyzed for these cats.

Exclusion criteria

Cats were excluded from the study if they did not meet inclusion criteria or if the medical record was incomplete, absent, or erroneous.

Procedures

Past medical history, signalment, physical examination findings, clinicopathologic test results including antigen testing for feline leukemia virus (FeLV) and antibody testing for feline immunodeficiency virus (FIV),[e] urinalysis, aerobic bacterial culture of urine obtained by cystocentesis, thyroid hormone concentration, abdominal ultrasonographic findings, cytology or histopathology, treatment, outcome, and necropsy results were recorded from cats with DKA meeting the inclusion criteria. Findings are reported from the time of initial examination at the teaching hospital, and all testing was performed at the teaching hospital. Follow-up and historical information regarding other DKA episodes of the study cats was recorded when available.

Cats were treated with an intravenous (IV) continuous rate infusion (CRI) of regular (Humulin-R)[f] insulin added to 240 mL of 0.9% NaCl at a concentration of 1.1 U/kg body weight or 2.2 U/kg body weight, depending on clinician preference.[5] The solution was administered at a rate of 10 mL/h for the first 2 hours and adjusted every 2 hours, as previously described, depending on blood glucose concentration (Table 1).[8,9] Initial concentration of regular insulin and information pertaining to insulin concentration adjustments were recorded.

Clinicopathologic findings and concurrent disease

Total serum potassium, phosphorus, magnesium, and blood pH were recorded at the time of initial

Table 1: Adjustable intravenous constant rate infusion protocol of regular insulin treatment and dextrose supplementation for cats with diabetic ketoacidosis[8,9]

Blood glucose concentration mmol/L (mg/dL)	Solution to fulfill fluid requirements	Rate of administration of insulin solution (mL/h)*
> 13.9 (250)	0.9% NaCl	10
11.1–13.9 (200–250)	0.9% NaCl + 2.5% dextrose	7
8.3–11.0 (150–199)	0.9% NaCl + 2.5% dextrose	5
5.5–8.2 (100–149)	0.9% NaCl + 5% dextrose	5
<5.5 (100)	0.9% NaCl + 5% dextrose	Stop insulin infusion

*Insulin solution composed of 1.1 U/kg or 2.2 U/kg of regular insulin added to a 240 mL bag of 0.9% NaCl.

examination.[a] The time (TK_{min}, TP_{min}, TMg_{min}, TpH_{min}) and value (K_{min}, P_{min}, Mg_{min}, pH_{min}) of the lowest electrolyte concentration and venous pH during the entire hospitalization period were also recorded. Venous pH, lactate concentration, ionized magnesium, ionized calcium, base deficit, bicarbonate, and blood glucose concentration were analyzed at the time of initial examination with a point-of-care analyzer.[b] Results of complete blood counts and serum biochemistry screens are also reported.[a] Special attention was paid to the diagnoses of diseases previously reported as common in cats with DM.[1,2] Acute pancreatitis, hepatic lipidosis, and chronic kidney disease were diagnosed according to the criteria in Table 2.[10–13]

Outcome variables

The time interval from initial examination at presentation until the time of administration of subcutaneous (SC) insulin, length of hospitalization, and survival were recorded. A poor outcome was defined as death, either as the cat succumbed to disease or by euthanasia. A good outcome was assigned to cats that were discharged alive from the hospital, except if cats were transferred directly to another veterinarian for further care or if cats were taken home against medical advice. Data from cats that were transferred directly to another veterinarian or were taken home against medical advice were excluded from the outcome analysis, although other variables associated with these cats are reported.

Table 2: Diagnoses of concurrent diseases in cats with diabetic ketoacidosis

Disease	Clinical signs	Clinicopathologic findings	Histopathology	Cytology	Ultrasonographic findings
Criteria for diagnosis					
Acute pancreatitis	Anorexia, lethargy, vomiting, diarrhea, or weight loss.	Feline pancreatic lipase immunoreactivity (fPLI>12 μg/L).[g]	Neutrophilic inflammation associated with interstitial edema and necrosis of mesenteric fat.	Not applicable	Hypoechoic, enlarged, irregular pancreas surrounded by a hyperechoic mesentery with or without abdominal effusion.
Clinical signs and at least one of the other following criteria:					
Hepatic lipidosis	Anorexia, lethargy, vomiting, icterus, or weight loss	Increased alanine aminotransferase and alkaline phosphatase activities.	Variably sized clear vacuoles within the cytoplasm of hepatocytes along with canalicular bile stasis and no evidence of inflammatory or neoplastic infiltrate.	Hepatocytes with variably sized aggregates of clear vacuoles.	Not applicable
Clinical signs and clinicopathologic abnormalities and either cytology or histopathology					
Chronic kidney disease	Anorexia, lethargy, vomiting, or weight loss.	Creatinine > 177 μmol/L (2 mg/dL) and blood urea nitrogen > 11.4 mmol/L (32 mg/dL) for at least 72 hours of IV fluid therapy.	Not applicable	Not applicable	Not applicable
Clinical signs and clinicopathologic findings					

Data analysis

Continuous variables were assessed for normality using the Shapiro–Wilks test. Median and range are reported for all variables because most variables were not normally distributed. 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 logistic regression model was developed to evaluate the relationship between the sex status and being a diabetic while controlling for neuter status. Woolf's approximation was used to calculate the 95% confidence interval (CI) for the odds ratio (OR) developed from this model. A similar model was developed evaluating the influence of increasing insulin CRI concentration and its association with a poor outcome. A P value <0.05 was considered significant for all evaluations. All statistical analyses were performed using a statistical software package.[h]

Results

Case selection

Two hundred twenty records with a recorded diagnosis of DKA were initially identified but 127 cats were excluded due to the following reasons: undocumented ketonuria or ketonemia ($n = 39$), incomplete medical record ($n = 38$), blood gas analysis was not performed ($n = 38$), venous pH ≥7.35 ($n = 21$), absence of hyperglycemia ($n = 13$), undocumented ketonuria, ketonemia, and acidemia ($n = 12$), nondiabetics ($n = 2$), and 2 dogs miscoded as cats. Therefore, 93 cats met the criteria for inclusion into the DKA group. Six hundred eighty-two cats were identified for the DM signalment comparison group and 16,926 cats were identified for the nondiabetic signalment comparison group. None of the cats were included in both groups.

Signalment and history

Breeds of cats with DKA included 67 (82%) Domestic Shorthair cats, 7 (8%) Siamese, 2 (2%) each of Abyssinian, Burmese, Norwegian Forest Cat, and Domestic Longhair, 1 (1%) Himalayan, and 1 (1%) mixed breed cat. Breed was not recorded in 9 cats. Significant differences in breed and other signalment characteristics of cats with DKA and DM are reported in Table 3.

Forty-seven of 93 cats (50%) were diagnosed with DKA at the time of initial diagnosis of DM, and the others (46 cats, 50%) had been previously diagnosed and treated for DM. In cats previously diagnosed with DM, the median length of time between the diagnosis of DM and DKA was one week (range, 0.1–378 weeks). Eighty-four of 93 cats with DKA (90%) had lethargy, 68 (73%) had inappetence, 52 (56%) had weight loss, 48 (52%) had polyuria and polydipsia, 45 (48%) had vomiting, 11 (12%) had diarrhea, and 6 (6%) had polyphagia.

Physical examination findings

Eighty-two cats with DKA (88%) were considered dehydrated, 3 (3%) were assessed as adequately hydrated, and hydration status was not reported in the remaining 8 cats (9%). Fifty-two of the 88 (59%) cats that had subjective body condition assessment were underweight, 13 (15%) were of normal weight, 20 (23%) were overweight, and 3 (3%) were obese.

Neurologic abnormalities were documented in 58 of 93 cats with DKA (62%). Forty-one cats (46%) had dull mentation and 13 other cats (14%) were obtunded. Twenty-four cats (27%), including the 13 obtunded cats and 7 cats with dull mentation were recumbent. Five cats (6%) had a plantigrade stance, and one of these cats had a dull mentation.

Clinicopathologic findings

Results of complete blood counts performed in 76 cats with DKA are reported in Table 4. Neutrophilia or thrombocytopenia was not associated with presence of acute pancreatitis and neutrophilia was also not associated with presence of a urinary tract infection. Anemia was not related with serum phosphorus concentration.

Results of complete serum biochemistry screens performed in 76 cats with DKA are reported in Table 5. Initial serum potassium concentration was below the reference interval in 44 cats (58%) but hypokalemia was ultimately documented in 74 cats (97%) at least once during the hospitalization period. Median K_{min} was 2.6 mmol/L ([2.6 mEq/L], range 1.7–5.1 mmol/L [1.7–5.1 mEq/L]), and median TK_{min} was 17 hours from the time of initial examination (range, 0–190 h).[a]

Initial serum phosphorus concentration was below the reference interval in 25 cats (33%) but hypophosphatemia was ultimately documented in 49 cats (65%) at least once during the hospitalization period. Median P_{min} was 0.6 mmol/L ([2 mg/dL], range 0.3–2.4 mmol/L [0.8–7.5 mg/dL]), and median TP_{min} was 23.5 hours from the time of initial examination (range, 0–102 h).[a]

Initial total serum magnesium concentration was below the reference range in 6 of 42 cats (14%), but hypomagnesemia was ultimately documented in 32 of 42 cats (76%) at least once during the hospitalization period. Median Mg_{min} was 0.6 mmol/L ([1.5 mg/dL] range, 0.4–1.6 mmol/L [0.9–3.9 mg/dL]) and median TMg_{min} was 35 hours from the time of initial examination (range,

Table 3: Signalment and weight of cats with diabetic ketoacidosis (DKA), uncomplicated diabetes mellitus (DM), and nondiabetic disease

	Cats with DKA ($n = 93$)	Cats with uncomplicated DM ($n = 682$)	Cats with nondiabetic disease ($n = 16,926$)	*P* value
Median age (range, years)	9.4 (1–17.9)	11.6 (0.7–19.5)	4.5 (0.1–20)	$P < 0.0003$[a,b,c]
Abyssinian Breed	2	5	46	$P = 0.0007$[a] $P = 0.002$[c]
Siamese Breed	7	21	390	$P = 0.01$[a] $P = 0.038$[b]
Male (neutered and intact)	69	452	9,759	*$P < 0.0001$[d]
Female (neutered and intact)	24	230	7,167	
Neutered (male and female)	93	670	12,888	$P < 0.0001$[d]
Intact (male and female)	0	12	4,038	
Median body weight (range, kg)	4.4 (2.2–9.7)	5.4 (1.8–10.9)	4.2 (1–16.8)	$P < 0.0003$[b,c]

[a]Significant difference detected between cats with DKA and nondiabetic cats.
[b]Significant difference detected between cats with DKA and cats with DM.
[c]Significant difference detected between cats with DM and nondiabetic cats.
[d]Significant difference detected between all cats with diabetes (DM and DKA combined) and nondiabetic cats.
*When controlling for neuter status, male cats were still more likely to have diabetes than females.

0–144 h). Total initial serum magnesium concentration was positively correlated with creatinine concentration and also with ionized magnesium concentration (Table 5 and Table 6, $P = 0.0004$ and $P = 0.001$, respectively).[a]

Median initial venous pH in 93 cats was 7.193 (range, 6.941–7.349, Table 6). Venous blood pH decreased further in 55 of 84 cats (66%) in which blood gas analysis was repeated during the course of hospitalization. Median pH_{min} was 7.142 (range, 6.834–7.332), and median TpH_{min} was 8 hours from the time of initial examination (range, 0–192 h). There was a significant inverse association between low venous pH and increased ionized magnesium as well as increased BUN concentration ($P = 0.02$ and $P = 0.01$, respectively). There was no significant association between venous pH and lactate, creatinine, total magnesium, or ionized calcium concentrations.

Urine acetoacetate concentration was greater than 1.5 mmol/l (15 mg/dL) in all 84 cats in which a urinalysis was performed. Serum acetoacetate concentration was > 1.5 mmol/L (15 mg/dL) in all 9 cats in which urine was not analyzed.[d] Aerobic urine culture was performed in 73 of 93 cats (78%). Ten of 73 cats (14%) had aerobic bacterial growth and 63 cats (86%) had no aerobic bacterial growth on urine culture. *Escherichia coli* was the most common bacteria cultured (in 8 of 10 cats, 80%).

Concurrent conditions

Acute pancreatitis, hepatic lipidosis, and chronic kidney disease were diagnosed in 32 (34%), 12 (13%), and 12 (13%) cats with DKA, respectively. Overall, 51 of 93 cats (55%) with DKA had acute pancreatitis, hepatic

Table 4: Complete blood counts in 76 cats with diabetic ketoacidosis*

Variable	Median	Range	Above RI	Normal	Below RI	Reference interval (RI)
RBC 10^{12}/L ($10^6/\mu L$)	7.5 (7.5)	2.6–11.3 (2.6–11.3)	1 (1%)	54 (71%)	21 (28%)	6.6–11.2 (6.6–11.2)
Hb g/L (g/dL)	117 (11.7)	40–160 (4–16)	1 (1%)	46 (61%)	29 (38%)	106–156 (10.6–15.6)
Hct (%)	34.5	12.3–55	2 (3%)	47 (62%)	27 (35%)	31.7–48
MCV (fL)	45.9	39.2–56	2 (3%)	74 (97%)	0 (0%)	36.7–53.7
MCHC (fL)	32	15.1–42.8	11 (14%)	56 (74%)	9 (12%)	30.1–35.6
Platelets* 10^{12}/L ($10^6/\mu L$)	244.5	64.8–609	6 (9.5%)	47 (73.5%)	11 (17%)	175–500
WBC 10^{12}/L ($10^6/\mu L$)	16.8	2.2–39.2	35 (46%)	40 (53%)	1 (1%)	4.0–18.7
Neutrophils 10^{12}/L ($10^6/\mu L$)	15.3	1.6–36.4	41 (54%)	34 (45%)	1 (1%)	2.3–14.0
Band neutrophils 10^{12}/L ($10^6/\mu L$)	0	0–1.8	17 (22%)	59 (78%)	0 (0%)	0
Lymphocytes 10^{12}/L ($10^6/\mu L$)	0.7	0–8.1	1 (1%)	30 (39.5%)	45 (59.5%)	0.8–6.1
Monocytes 10^{12}/L ($10^6/\mu L$)	0.4	0–3.9	29 (38%)	47 (62%)	0 (0%)	0–0.7
Eosinophils 10^{12}/L ($10^6/\mu L$)	0.2	0–2.3	2 (3%)	74 (97%)	0 (0%)	0–1.5

*Platelet count was reported in only 64 cats.
Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin volume; WBC, white blood cell; RBC, red blood cell; RI, reference interval.

Table 5: Serum biochemistry results in 76 cats with diabetic ketoacidosis*, **

Variable	Median	Range	Above RI	Normal value	Below RI	Reference interval
Glucose mmol/L (mg/dL)*	18.6 (335)	14.4–55.8 (259–1,006)	68 (91%)	8 (9%)	0 (0%)	3.7–9.3 (67–168)
Blood urea nitrogen mmol/L (mg/dL)	12.8 (36)	3.2–69.3 (9–194)	41 (54%)	24 (32%)	11 (14%)	5.3–11.4 (15–32)
Creatinine μmol/L (mg/dL)	141.4 (1.6)	61.9–610 (0.7–6.9)	23 (30%)	42 (55%)	11 (15%)	88.4–176.8 (1–2)
Phosphorus mmol/L (mg/dL)	1.2 (3.7)	0.4–5.3 (1.3–16.4)	12 (16%)	39 (51%)	25 (33%)	1–2.1 (3–6.6)
Total calcium mmol/L (mg/dL)	2.2 (8.7)	1.6–2.7 (6.3–10.9)	0 (0%)	22 (29%)	54 (71%)	2.3–2.8 (9.1–11.2)
Sodium mmol/L (mEq/L)	148 (148)	129–177 (129–177)	6 (8%)	43 (57%)	27 (35%)	146–157 (146–157)
Potassium mmol/L (mEq/L)	3.3 (3.3)	2.2–5.8 (2.2–5.8)	5 (7%)	27 (35%)	44 (58%)	3.5–4.8 (3.5–4.8)
Chloride mmol/L (mEq/L)	107 (107)	77–132 (77–132)	2 (3%)	8 (10%)	66 (87%)	116–126 (116–126)
Total CO_2 (mmol/L)	10	5–20	0 (0%)	12 (16%)	64 (84%)	16–25
Total protein g/L (g/dL)	69 (6.9)	36–88 (3.6–8.8)	2 (3%)	55 (72%)	19 (25%)	60–86 (6–8.6)
Albumin g/L (g/dL)	31 (3.1)	14–43 (1.4–4.3)	8 (10.5%)	60 (79%)	8 (10.5%)	24–38 (2.4–3.8)
Globulins g/L (g/dL)	36 (3.6)	22–54 (2.2–5.4)	2 (2.5%)	59 (77.5%)	15 (20%)	31–50 (3.1–5)
ALT U/L (units/L)	163 (163)	30–1,725 (30–1,725)	41 (54%)	34 (45%)	1 (1%)	33–152 (33–152)
AST U/L (units/L)	165 (165)	25–1,076 (25–1,076)	73 (96%)	3 (4%)	0 (0%)	1–37 (1–37)
ALP U/L (units/L)	61 (61)	18–753 (18–753)	19 (25%)	56 (74%)	1 (1%)	22–87 (22–87)
GGT U/L (units/L)	7 (7)	5–31 (5–31)	5 (7%)	71 (93%)	0 (0%)	5–19 (5–19)
Total bilirubin μmol/L (mg/dL)	17.1 (1)	3.4–227.4 (0.2–13.3)	45 (59%)	31 (41%)	0 (0%)	1.7–13.7 (0.1–0.8)
Cholesterol mmol/L (mg/dL)	7.1 (274)	2.7–23.5 (105–906)	46 (61%)	30 (39%)	0 (0%)	2.5–6.4 (96–248)
Calculated osmolarity (mOsm/L)	208	20–413	39 (51%)	28 (37%)	9 (12%)	287–307
Anion gap mmol/L (mEq/L)	33 (33)	4.2–50 (4.2–50)	75 (99%)	0 (0%)	1 (1%)	12–16 (12–16)
Total magnesium** mmol/L (mg/dL)	1.1 (2.6)	0.4–2.6 (1–6.4)	20 (48%)	16 (38%)	6 (14%)	0.8–1.1 (1.9–2.6)

*Cats that had a normal blood glucose concentration on the chemistry screen had high blood glucose concentration (> 13.9 mmol/L [250 mg/dL]) documented by a point of care analyzer or glucometer.[b,c]

**Total magnesium is reported in 42 cats.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CO_2, carbon dioxide; GGT, gamma-glutamyl transferase; RI, reference interval.

lipidosis, chronic kidney disease, or a urinary tract infection. Some cats had more than one concurrent condition. Presence of acute pancreatitis, hepatic lipidosis, chronic kidney disease, or inflammatory bowel disease was not associated with whether the cat had new or previously diagnosed DM. Retroviral testing was performed in 33 cats. All cats tested negative for FeLV and 3 cats tested positive for FIV. Thyroid hormone concentration was low or normal in all 17 cats in which it was measured (median 14.2 nmol/L [1.1 μg/dL], range 2.6–24.5 nmol/L [0.2–1.9 μg/dL]). Inflammatory bowel disease was histopathologically confirmed in 4 cats.

Treatment

Eighty-nine cats with DKA (96%) received IV fluid therapy. The remaining 4 cats were euthanized upon diagnosis of DKA. The most common fluid type administered to 70 cats (78%) was an isotonic-balanced electrolyte solution (Normosol-R). Eighty of 89 cats (90%) received continuous IV potassium supplementation, 52 of 89 cats (58%) received continuous IV phosphorus supplementation, 38 of 89 cats (43%) received continuous IV magnesium supplementation, and 33 of 89 cats (37%) received IV sodium bicarbonate therapy. Cats that received IV sodium bicarbonate therapy had significantly lower venous pH (mean 7.16 ± .078, median 7.149, range 6.96–7.34) compared to cats that did not receive IV sodium bicarbonate therapy (mean 7.22 ± .093, median 7.24, range 6.94–7.349, $P < 0.001$).

Eighty-nine cats (96%) received an IV CRI of regular (Humulin-R) insulin for a median duration of 45 hours (range, 1–256 h). However, data regarding the

Table 6: Venous blood gas results in cats with diabetic ketoacidosis

Variable	No. Tested	Median	Range	Above RI	Normal value	Below RI	Reference Interval
Venous pH	93	7.193	6.941–7.349	0 (0%)	0 (0%)	93 (100%)	7.35–7.47
iCa2+ mmol/L	92	1.135	0.82–1.38	3 (3%)	53 (58%)	36 (39%)	1.13–1.33
iMg2+ mmol/L	75	0.485	0.21–0.85	51 (68%)	22 (29%)	2 (3%)	0.24–0.41
HCO3- mmol/L (mEq/mL)	93	12.8 (12.8)	6.5–22.9 (6.5–22.9)	0 (0%)	4 (4%)	89 (96%)	20–24 (20–24)
Base deficit	93	–12.5	–3.1 to –25.7	0 (0%)	1 (1%)	92 (99%)	–4 to +4
Lactate mmol/L	87	1.8	0.1–6.3	16 (18.5%)	68 (78%)	3 (3.5%)	0.6–2.5

iCa, ionized calcium; iMg, ionized magnesium; HCO_3, bicarbonate; RI, reference interval.

dose of insulin administered were available in only 59 of these cats. Forty-nine of 59 cats (83%) and 10 of 59 cats (17%) were treated with an initial concentration of 1.1 or 2.2 U/kg/240 mL bag of 0.9% NaCl, respectively. The concentration of insulin was increased over the course of treatment in 20 cats, 18 of which received an initial insulin concentration of 1.1 U/kg/240 mL bag of 0.9% NaCl. The initial insulin concentration was not decreased in any of the cats. Cats treated with a higher concentration of insulin were less likely to have a poor outcome compared to cats treated with a lower concentration of insulin (OR 0.14, 95% CI: 0.02–1.16, $P = 0.02$). There was no significant association between the initial insulin concentration administered and median K_{min}, P_{min}, or Mg_{min}.

Outcome of cats with DKA

Fifty-seven of 93 cats (61%) were discharged from the hospital. Four of these 57 cats (7%) were transferred to a referring veterinarian for further care, and 3 additional cats (5%) were taken home against medical advice. These 7 cats were not included in the statistical analysis for variables associated with outcome. Fifty of 93 cats (54%) with a good outcome had a median hospitalization length of 6.5 days (range, 1–15 days) and a median time from admission until intermediate-acting SC insulin was administered of 82 hours (range, 6–260 h). Eleven cats had at least 1 additional episode of DKA after the study period, 4 other cats had DKA episodes prior to the study period, and 2 other cats had additional DKA episodes prior to and after the study period. None of the cats had 2 episodes of DKA during the study period. Overall, 17 of 93 cats (18%) had recurrent DKA episodes. Thirty-three cats (35%) were euthanized after a median hospitalization length of 1 day (range, 0–9 days). Four of the 33 euthanized cats (12%) had previous episodes of DKA. Three other cats (3/93, 3%) died during the first 24 hours of hospitalization.

Poor outcome was significantly associated with increased initial creatinine, BUN, or total serum magnesium concentration ($P = 0.007$, $P = 0.005$, or $P = 0.03$, respectively). Poor outcome was also significantly associated with increased initial total bilirubin concentration ($P = 0.03$). There was no association between outcome and prior diagnosis of DM or newly diagnosed DM, neurologic abnormalities, presence of acute pancreatitis, hepatic lipidosis, chronic renal disease, urinary tract infection, serum bicarbonate concentration, base excess, venous pH, osmolarity, hematocrit, neutrophil or platelet count, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase activities, cholesterol, initial total serum calcium, ionized calcium, potassium, ionized magnesium, sodium, or phosphorus concentrations, or administration of sodium bicarbonate. There was also no association between length of hospitalization and the initial insulin concentration administered.

Postmortem examination

Gross and histologic postmortem examinations were performed in 11 of the 36 cats (31%) that died or were euthanized. Histopathologic changes were noted in the pancreas of all 11 cats and included nodular hyperplasia (8 cats), pancreatic islet amyloidosis (5 cats), peripancreatic fat necrosis (3 cats), pancreatic islet vacuolization (2 cats), acute pancreatitis (1 cat), and lymphocytic interstitial pancreatitis (1 cat). All 11 cats had evidence of renal changes on histopathology. Six cats had tubulointerstitial nephritis, 4 cats had interstitial nephritis, and 3 cats had tubular necrosis. Ten cats had diffuse fatty change in the liver. Other necropsy findings were noted in 1 cat only.

Discussion

Siamese cats were identified to be at increased risk for DKA when compared to cats with uncomplicated DM and cats with nondiabetic disease, whereas Abyssinian cats were found to be at increased risk for DM and DKA when compared to cats with nondiabetic disease. To the authors' knowledge this is the first report of a particular breed of cat at increased risk specifically for DKA, and the first report indicating that Siamese and Abyssinian cats are at increased risk for diabetes. Other breed studies of cats have reported that Burmese cats are at increased risk for DM in Australia and the United Kingdom and that pure breed cats are at increased risk for DM in the United States.[14–16] Breed predisposition suggests that genetic factors unique to Siamese cats may influence the development of DKA and that genetic peculiarities of Abyssinian cats may increase their risk for DM and therefore also for DKA. Distinguishing genetic characteristics associated with specific other diseases in Siamese and Abyssinian cats have already been published.[17,18] As genomic data of cats become available in the future, a possible genetic risk for DKA or DM in Siamese or Abyssinian cats may be detected.

Poor outcome was significantly associated with increased initial creatinine, BUN, or total serum magnesium concentration. Creatinine and total magnesium concentrations were also positively correlated with one another, suggesting that decreased renal clearance led to increased total magnesium concentration. These findings suggest that renal dysfunction is associated with poor outcome in cats with DKA, however, chronic renal

failure, as defined in this study, was not significantly associated with outcome. This may be due to this study's definition of chronic renal failure that required presence of azotemia after at least 72 hours of IV fluid therapy. It is possible that some cats that had chronic renal failure were not defined as such by this study because median hospitalization length prior to death or euthanasia was 24 hours, and some cats with chronic renal failure may not have survived 72 hours. However, initial creatinine, BUN, or total serum magnesium concentration were reported in a large number of cats, and therefore allowed for detection of a significant finding suggesting that renal dysfunction is associated with poor outcome. This study's definition of chronic renal failure, which required presence of azotemia after at least 72 hours of IV fluid therapy, may have also resulted in misclassification of cats with acute renal failure or persistent prerenal azotemia, as cats with chronic renal failure. Prospective studies will be needed to determine whether azotemia or total serum magnesium concentration are associated with a poor outcome in cats with DKA due to chronic or acute renal disease, prerenal azotemia, or other factors.

Total bilirubin concentration was also associated with poor outcome, although acute pancreatitis and hepatic lipidosis were not found to increase the risk of a poor outcome. This may be due to the fact that total bilirubin was quantified in a far larger number of cats than the number of cats in which results of abdominal ultrasound, feline pancreatic lipase immunoreactivity, liver cytology, or histopathology were available for review. Total bilirubin concentration had more statistical power to detect a difference between cats with a good or poor outcome than did a confirmed diagnosis of acute pancreatitis or hepatic lipidosis. It is therefore concluded that high total bilirubin concentration is associated with a poor outcome in cats with DKA, although prospective studies will be needed to determine whether this association is due to acute pancreatitis, hepatic lipidosis, or other factors such as sepsis or intrahepatic cholestasis.

Over half of the cats with DKA had a confirmed diagnosis of acute pancreatitis, hepatic lipidosis, chronic kidney disease, or a urinary tract infection. Acute pancreatitis is identified here, for the first time, as the most common concurrent disorder in cats with DKA. Presence of concurrent disease is thought to contribute to the development of DKA in diabetics, and treatment of concurrent disease is likely to improve the outcome of cats with DKA. Therefore, a knowledge of which disorders occur most commonly in cats with DKA may help focus diagnostic investigations and therapeutic interventions on the concurrent disorders most likely to be present in such cats.

The outcome of cats improved significantly as the administered concentration of IV insulin CRI increased from 1.1 to 2.2 U/kg/240 mL bag of 0.9% NaCl. There was also no significant association between the initial insulin concentration administered and median K_{min}, P_{min}, or Mg_{min}, indicating that administration of an initial high concentration of insulin does not result in more significant electrolyte imbalances. Similarly, the initial administered insulin concentration was not associated with length of hospitalization.

The findings in this study suggest that an initial insulin concentration of 2.2 U/kg/240 mL bag of 0.9% NaCl may be preferred over 1.1 U/kg/240 mL 0.9% NaCl when treating cats with DKA using the regimen outlined in Table 1. However, a prospective study is needed to confirm these findings. The reason for improved outcome with a higher IV insulin CRI dose may be that the lower dose is simply ineffective. The dose of 2.2 U/Kg/240 mL given at 10 mL/h is equivalent to 0.09 U/kg/h, and is similar to the initial standard of care insulin dose used in people and dogs with DKA.[9,19] It is possible that cats require this same dose. It is also possible that the initial dose of 2.2 U/kg/240 mL bag of 0.9% NaCl resulted in a better outcome because other properties of insulin, such as its anti-inflammatory effect, improved the outcome at the higher dose.[20,21]

Although not all cats had electrolyte deficiencies at the time of initial examination, most cats developed electrolyte imbalances over the course of hospitalization. Electrolyte and pH imbalances worsened within the first 35 hours of treatment, despite electrolyte supplementation and sodium bicarbonate therapy. These imbalances were not associated with the initial insulin concentration administered. Based on these findings, it may be prudent to perform frequent measurement of electrolyte concentrations, especially during the first 35 hours of treatment.

It is important to note that while 33 of 89 cats (37%) received IV sodium bicarbonate therapy, this finding is reported retrospectively, and not as an endorsement for bicarbonate treatment in cats with DKA. While no clear guidelines for bicarbonate treatment have been established in cats, the American Diabetes Association recommends bicarbonate treatment in people with DKA only if their venous pH remains below 7.0 after initial fluid resuscitation.[19] Bicarbonate treatment in people with DKA is controversial because it may increase the risk for fatal cerebral edema and hypokalemia.[22,23]

This study is limited by its retrospective nature and many questions regarding DKA in cats remain unanswered. In addition to inability to definitively diagnose all concurrent disorders, the rational for treatment decisions may not be apparent, retrospectively. For example,

some of the cats that received bicarbonate treatment appear to have only mild acidemia at the time of initial examination. However, venous pH decreased further in most cats, and was likely lower at the time that bicarbonate was administered. Similarly, the choice of whether to use 1.1 or 2.2 U/kg/240 mL bag of 0.9% NaCl that was assumed to be clinician dependent and random may have been influenced by unknown factors such as perceived severity of patient illness or sodium and chloride concentration. Furthermore, while the starting concentration of insulin CRI was noted in the record, times in which the insulin CRI was discontinued due to IV catheter malfunction or other reasons were not clearly delineated in the medical records and this prevented a calculation of the total dose of insulin that each cat received. Also, the time in which insulin CRI was begun, is not reported. Furthermore, cats were included in the group of uncomplicated DM only if they had documented absence of ketonuria and a venous pH ≥7.35. This was done to ensure that cats with DKA were excluded from the group of uncomplicated DM. However, these inclusion criteria may have selected for a relatively healthy diabetic population, as cats with acidemia due to reasons other than ketonuria may have been excluded from the group of cats with uncomplicated DM. Another study limitation is that a large number of variables was analyzed for a possible association with outcome. Analysis of a large number of variables may result in a type I statistical error in which a significant difference is detected erroneously. This approach is recommended for initial studies of a topic, such as this study. Once initial data regarding risk factors for DKA in cats are known, more focused studies can be designed to confirm or refute the present findings.

In summary, DKA is a diabetic complication with a guarded prognosis as 39% of cats have a poor outcome, and 18% of cats have recurrent DKA episodes. Lack of insulin treatment or short duration of insulin treatment is common in cats with DKA and many cats with DKA have a concurrent disorder. Cats with DKA are more likely to be young, Siamese, and without increased body weight compared to cats with uncomplicated DM. Male and Abyssinian cats are at increased risk for DM, and are therefore also overrepresented among cats with DKA. Poor outcome is significantly associated with increased initial creatinine, BUN, total serum magnesium, or total bilirubin concentration. Good outcome was associated with a higher initial concentration of IV insulin CRI.

Footnotes

[a] Chemistry analyzer, Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY.
[b] Stat Profile, NOVA Biomedical Corporation, Waltham, MA.
[c] Accu-chek, Roche Diagnostics Corp, Indianapolis, IN.
[d] Urinalysis N-Multistix SG, Bayer Corporation, Elkhart, IN.
[e] Feline leukemia virus antigen/Feline immunodeficiency virus antibody test, IDEXX, Westbrook, ME.
[f] Humulin R, Eli Lilly and Co, Indianapolis, IN.
[g] Spec fPL (feline pancreas-specific lipase) assay, IDEXX.
[h] Stata 11.0 for Windows, Stata Corporation, College Station, TX.

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