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Pancreatic Lipase Immunoreactivity in Serum of Dogs with Diabetic Ketoacidosis

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Background: Diabetic ketoacidosis (DKA) is a relatively common endocrine disorder in dogs and is routinely associated with concurrent pancreatic injury.

Objectives: The aims of this study were to determine the prevalence of pancreatic injury in dogs with DKA based on measurement of pancreatic lipase immunoreactivity in serum (PLI); compare demographic, clinicopathologic, and ultrasonographic findings in dogs with and without evidence of concurrent pancreatic injury; determine the impact of pancreatic injury on duration of hospitalization and short-term outcome.

Animals: One hundred and nineteen dogs with DKA with or without concurrent pancreatic injury.

Methods: Retrospective study. Dogs with DKA were divided into three groups on the basis of PLI results: positive for pancreatic injury (PLI_{pos}), negative for pancreatic injury (PLI_{neg}), and not tested (PLI_{na}). Demographics, clinicopathologic test results, findings on abdominal ultrasonography (AUS), duration of hospitalization, and short-term outcome were compared between the three groups.

Results: Based on serum PLI activity, 45 dogs (73%) with DKA had evidence of concurrent pancreatic injury. Median total carbon dioxide was significantly lower in the PLI_{pos} dogs compared to the PLI_{neg} dogs. There was fair agreement ($\kappa = 0.26$) between serum PLI activity and AUS. Evidence of pancreatic injury was not associated with significantly longer periods of hospitalization (PLI_{pos} median 6 days, range 4–7 days, PLI_{neg} median 4 days, range 3–6 days) and did not influence short-term outcome (PLI_{pos} failure to survive to discharge 11/45, 24%, PLI_{neg} failure to survive to discharge 2/17, 12%).

Clinical Importance: Concurrent pancreatic injury is common in dogs with DKA, but did not affect prognosis in this population of dogs.

Key words: Canine; Diabetes mellitus; Outcome; Pancreatitis.

Diabetic ketoacidosis (DKA) is a severe and potentially fatal complication of diabetes mellitus (DM) and is characterized by hyperglycemia, hyperketonemia or ketonuria, and metabolic acidosis.[1–3] Prolonged absolute or relative insulin deficiency results in accelerated lipolysis, hypertriglyceridemia, and ketone body production.[1–3] When ketone production exceeds peripheral utilization, the associated hydrogen ions overwhelm the body's buffering systems.[3] Severe metabolic acidosis and electrolyte imbalances ensue.

Abbreviations:

DM	diabetes mellitus
DKA	diabetic ketoacidosis
PLI	pancreatic lipase immunoreactivity
AUS	abdominal ultrasonography
PLI_{pos}	pancreatic injury positive
PLI_{neg}	pancreatic injury negative
PLI_{na}	PLI not performed

Dogs with DKA routinely present with anorexia and vomiting, and are typically lethargic and dehydrated.[1,2] Concurrent disorders, such as pancreatitis, urinary tract infection, hyperadrenocorticism, and neoplasia are often reported.[1–4] These conditions can decrease insulin sensitivity through the release of counterregulatory hormones and inflammatory cytokines.[5]

Pancreatitis is routinely diagnosed in people with DKA on the basis of clinical signs, activity of serum amylase, lipase, or both more than three times the upper limit of the reference intervals, increased serum alanine transaminase activity, and pancreatic enlargement, edema, or both on contrast-enhanced computed tomography of the abdomen.[6,7] Twenty percent of people with DKA develop severe or life-threatening pancreatitis requiring prompt diagnosis and aggressive management.[6] The specific trigger(s) for pancreatitis associated with DKA are unclear; however, hypertriglyceridemia likely plays a key role. Hypovolemia-induced ischemia is likely contributing factor to pancreatic injury in dogs with DKA because of its high blood flow requirement and intrinsic susceptibility to ischemia.[8]

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In both dogs and people, the clinical signs associated with DKA and pancreatitis are similar, making a clinical diagnosis of pancreatitis challenging. Definitive diagnosis in both species requires histological evaluation of pancreatic tissue, however, this procedure is rarely performed due to concerns for human and dog safety. In animals, a clinical diagnosis of pancreatitis relies upon consistent clinical signs, such as anorexia, vomiting, or abdominal pain, in conjunction with supportive findings on abdominal ultrasonography (AUS) or documentation of increased pancreatic lipase immunoreactivity (PLI).[1,5,9] Acute pancreatitis is the most prevalent concurrent disorder in dogs with DKA, and occurs in 40% of dogs with DKA.[3] Although it did not appear to impact outcome, assessed as survival to discharge or euthanasia, dogs with pancreatitis required longer periods of hospitalization.[3] The diagnosis of pancreatitis was based on AUS (38%; 48/127 dogs) or necropsy findings (5%; 6/127 dogs)[3] and likely underestimated the true prevalence of concurrent pancreatitis, as AUS has only moderate diagnostic sensitivity for this disease.[10,11]

The aims of this study were: (1) determine the prevalence of pancreatic injury in dogs with DKA based on PLI measurement; (2) compare demographic information, clinicopathologic data, and findings on AUS for dogs with and without evidence of pancreatic injury; and (3) determine the impact of concurrent pancreatic injury on duration of hospitalization and short-term outcome (ie, survival to discharge).

Materials and Methods

Criteria for Selection of Cases

The medical records database at the Texas A&M College of Veterinary Medicine and Biomedical Sciences Veterinary Medical Teaching Hospital was searched for dogs diagnosed with DKA between January 2002 and September 2014. The coded diagnosis of DKA was verified by documentation of hyperglycemia (reference interval: 83–112 mg/dL[a] or 60–135 mg/dL[b]), metabolic acidosis (total carbon dioxide ≤20 mmol/L; reference interval: 21–28 mmol/L[b]; or blood pH <7.35; reference interval: 7.38–7.49[a]), and ketonuria (based on urine dipstick analysis[c]) within 6 hours of admission to the hospital.

Only the first admission within this time period was included for dogs admitted more than once.

Signalment, body weight, duration of hospitalization (days from admission to discharge), and short-term outcome (euthanized/died or discharged) were recorded for each case.

Serum PLI Measurement. Serum was collected within 6–12 hours of admission and stored at 2–8°C for up to 3 days before analysis. Two validated ELISAs were used for determination of the PLI.[12,13] Before 2006, an in-house assay was utilized (2.2–102.1 μg/L is normal; >200 μg/L is consistent with pancreatic injury)[12]; after 2006, a commercial ELISA[d] was used (0–200 μg/L is normal; 200–400 μg/L is "grey range"; >400 μg/L is consistent with pancreatic injury).[13] A PLI >200 μg/L (before 2006) and 400 μg/L (after 2006) respectively was considered indicative of pancreatic injury (PLI_{pos}); results below these levels were considered not supportive of pancreatic injury (PLI_{neg}).

Clinicopathologic Findings. Results of routine clinicopathologic tests including venous blood gas analysis,[a] complete blood count (CBC),[e] serum biochemical profile,[b] urinalysis,[c] and coagulation testing[f] were recorded for each case, when available.

Venous blood pH and plasma lactate, bicarbonate and ionized calcium concentrations were determined with a point-of-care analyzer.[a]

Abdominal Ultrasonography. Findings on AUS were recorded when available.[g] Positioning of the dog was decided by the radiologist, but the pancreas was routinely viewed via a ventral abdominal approach. In deep chested dogs, a right intercostal approach was occasionally used to visualize the right lobe. A written report was generated within 24–48 hours of the examination. Findings were indicative of acute pancreatitis if an enlarged, irregular, or hypoechoic pancreas in conjunction with a hyperechoic peripancreatic mesentery or fat was reported.[14] Additional supportive findings included corrugation of the duodenum, a distended, hypomotile stomach or duodenum, peripancreatic effusion, or extrahepatic bile duct obstruction.[14] Findings indicative of chronic pancreatitis included a small, hyperechoic, or nodular pancreas. The pancreas was presumed to be ultrasonographically unremarkable if it was not specifically described.

Statistical Analysis. Dogs were retrospectively categorized into one of three groups for statistical analysis: PLI_{pos}, PLI_{neg}, and PLI not performed (PLI_{na}). Data were assessed for normality by evaluating descriptive statistics, plotting histograms, and performing the Anderson-Darling normality test within statistical software.[h] Data violating the normality assumption were transformed before statistical analysis using the natural logarithm or by ranking when the log transformation did not improve the distributional form. Quantitative data were descriptively presented as median and interquartile range due to the small sample sizes in some groups and the apparent violation of the normality assumption for a number of analyzed outcomes. Quantitative data were compared between groups using 1-way ANOVA with Bonferroni adjustment of P values for posthoc pairwise comparisons. Categorical variables were compared using chi-square or Fisher exact tests. Agreement between AUS and PLI was estimated using the kappa statistic. Statistical analysis was performed using commercially available software[i] and results interpreted at the $P < .05$ level of significance.

Results

Prevalence of Concurrent Pancreatic Injury in Dogs with DKA

Between January 2002 and September 2014, 119 dogs met the diagnostic criteria for DKA. Sixty-two cases were screened for pancreatic injury by PLI quantitation. Of these, 45 (71%) had a PLI result consistent with pancreatic injury (PLI_{pos}), while 17 (27%) had a PLI result that was not supportive of pancreatic injury (PLI_{neg}). The remaining 57 cases were not screened for pancreatic injury using this modality (PLI_{na}).

Demographics, Clinicopathologic Testing, and AUS Findings

There was no apparent age, body weight, sex, or breed differences between the three groups. Median age in the PLI_{pos}, PLI_{neg}, and PLI_{na} groups was 9, 8, and 8 years, respectively ($P = .64$). Median body weight in the PLI_{pos}, PLI_{neg}, and PLI_{na} groups was 8, 7, and 12 kg, respectively ($P = .21$). Male and female dogs were equally represented in each group; 24 male and 21 female in the PLI_{pos} group, 8 male and 9 female in the PLI_{neg} group, and 28 male and 29 female in the PLI_{na} group. The most common breeds represented in each

group were the Labrador retriever (PLI_{pos} 7%, PLI_{neg} 5%, PLI_{na} 9% and mixed-breed dog (PLI_{pos} 13%, PLI_{neg} 12%, PLI_{na} 19%). Five miniature schnauzers were present in the study population, with four of them being in the PLI_{pos} group. The fifth dog was in the PLI_{na} group.

Results of CBCs (Table 1), biochemistry profiles (Table 2), coagulation profiles (Table 3), and urinalyses (Table 4) are provided for dogs in the PLI_{pos}, PLI_{neg}, and PLI_{na} groups. The median band neutrophil count was significantly higher in the PLI_{pos} group compared to the PLI_{neg} group ($P = .001$). The median serum glucose concentration was significantly higher in the PLI_{na} group compared to the PLI_{neg} group ($P = .03$), and the median total carbon dioxide was significantly lower in the PLI_{pos} group compared to the PLI_{neg} group ($P = .02$). No significant differences were detected between any groups on the coagulation profile and urinalysis.

Of the 62 cases screened for pancreatic injury by PLI quantification, 57 underwent AUS (44/45 in the PLI_{pos} group and 13/17 in the PLI_{neg} group). Findings on AUS for the PLI_{pos} group suggested acute pancreatitis in 28 dogs and chronic pancreatitis in three dogs. No ultrasonographic abnormalities were detected in 13 dogs. Findings on AUS for the PLI_{neg} group suggested acute pancreatitis in 5 dogs; no abnormalities on ultrasonographic examination were detected in the other 8. AUS and PLI were in agreement regarding pancreatic injury for 70% (31/44) of dogs in the PLI_{pos} group and 47% (8/17) of dogs in the PLI_{neg} group. Overall agreement between AUS and PLI was fair ($\kappa = 0.26$; 0.01–0.52; $P = .036$).

Impact of Concurrent Pancreatic Injury on Dog Outcome

The median duration of hospitalization for dogs in the PLI_{na} group was 3 days, which was significantly shorter than for dogs undergoing PLI measurement (n = 62, $P < .001$). However, the median duration of hospitalization for the PLI_{pos} dogs (6 days, range 4–7 days) was not significantly longer than for the PLI_{neg} group (4 days, range 3–6 days).

Eleven dogs in the PLI_{pos} group did not survive to discharge (24%; 2 died, 9 euthanized), and 2 dogs in the PLI_{neg} group did not survive (12%; both died). Over half (30/57; 53%) of the PLI_{na} dogs did not survive to discharge; 3 died and 27 were euthanized. Twenty of these 27 were euthanized within 6 hours of admission. Dogs in the PLI_{na} group were significantly more likely to be euthanized ($P = .03$), but were not more likely to die ($P = .71$) compared to dogs in the PLI_{pos} group.

Discussion

This report describes PLI results in dogs with DKA and the impact of biochemical evidence of pancreatic injury on clinicopathologic findings and outcome. In this study, 45 dogs (73%) tested had evidence of pancreatic injury, suggesting that this is a common comorbidity in dogs with DKA. This proportion is substantially higher than that described in an earlier study (38%) in which an antemortem diagnosis of pancreatitis was based on AUS alone.[3] Despite a relatively high prevalence, no clinicopathologic variables aside from band neutrophil count and total carbon dioxide were significantly different between PLI_{pos} and PLI_{neg} dogs. Clinically, biochemical evidence of pancreatic injury did not affect outcome or significantly prolong the duration of hospitalization.

Although a definitive diagnosis of pancreatitis requires histological examination of affected tissue, this was not performed on any dogs in this study. However, this is rarely feasible in the clinical setting because of morbidity and the lack of specific treatment options. Furthermore, pancreatic inflammatory lesions might be localized and therefore overlooked with routine biopsy procedures.[15] Instead, a clinical diagnosis of pancreatitis is based on a combination of two or more findings, including history, predisposing factors such as hypertriglyceridemia, hypovolemia-induced ischemia, dietary indiscretion, or drug history, clinical signs including lethargy, anorexia, vomiting, or abdominal pain), and supportive evidence on noninvasive diagnostic testing. Using pancreatic

Table 1. CBC results of dogs with diabetic ketoacidosis (DKA).

Variable	Untested (n = 57)	cPLI negative (n = 17)	cPLI positive (n = 45)	Reference interval	*P* value[a]
WBC (10^4 cells/μL)[b]	1.53 (1.01–2.65)	1.57 (1.20–2.22)	1.93 (1.37–2.39)	0.6–17	.65
Segmented neutrophils (10^4 cells/μL)[b]	1.27 (0.80–2.12)	1.24 (1.04–1.94)	1.39 (1.09–2.08)	0.3–1.2	.75
Band neutrophils (cells/μL)[b]	0[a] (0–521)	0[b] (0–0)	206[a] (0–476)	0–300	.001
Lymphocytes (cells/μL)[b]	993 (533–1827)	822 (480–1257)	634 (458–1089)	1000–4800	.79
Monocytes (cells/μL)[b]	861 (530–2393)	1560 (654–1854)	1552 (1063–2124)	150–1250	.39
Eosinophils (cells/μL)[b]	0 (0–119)	0 (0–160)	0 (0–132)	100–1250	.72
Platelets (10^5 cells/μL)[b]	3.98 (3.02–5.56)	3.95 (3.05–6.04)	4.34 (3.36–5.74)	2.0–5.0	.81
RBC (10^6/L)	6.07 (5.27–6.54)	5.98 (5.62–6.76)	6.08 (5.13–6.75)	5.50–8.50	.60
Hb (g/dL)	13.3 (11.8–14.9)	13.8 (12.4–15.3)	13.5 (10.4–15.6)	10.0–20.0	.54
Hct (%)	40.0 (34.9–44.0)	40.9 (39.0–45.0)	43.0 (33.0–46.5)	31.0–56.0	.57

[a]Based on 1-way ANOVA comparing the three groups. Medians without superscripts in common were significantly different ($P < .05$) based on posthoc pairwise comparisons with Bonferroni correction of *P* values.

[b]Variable transformed prior to statistical analysis.

Table 2. Serum chemistry results in dogs with diabetic ketoacidosis (DKA).

Variable	Untested (n = 57)	cPLI negative (n = 17)	cPLI positive (n = 45)	Reference interval	*P* value[a]
Glucose (mg/dL)[b]	490[a] (374–609)	363[b] (294–473)	431[a,b] (348–572)	60–135	.030
Cholesterol (mg/dL)[b]	308 (216–431)	354 (267–539)	352 (279–414)	120–247	.12
BUN (mg/dL)[b]	22 (15–38)	17 (12–25)	30 (12–51)	5–29	.14
Creatinine (mg/dL)	0.9 (0.7–1.8)	0.7 (0.6–1.3)	1.0 (0.6–1.5)	0.3–2	.26
Magnesium (mg/dL)	2.0 (1.8–2.4)	2.0 (1.8–2.3)	2.1 (1.7–2.6)	1.7–2.1	.42
Calcium (mg/dL)[b]	9.5 (8.4–10.1)	9.6 (8.9–10.1)	9.0 (8.2–10.2)	9.3–11.8	.61
Phosphorus (mg/dL)[b]	5.4 (4.3–6.4)	5.2 (3.1–6.6)	4.7 (3.3–5.9)	2.9–6.2	.084
Total protein (g/dL)	6.6 (5.6–7.1)	6.6 (6.1–7.4)	6.6 (5.7–7.2)	5.7–7.8	.48
Albumin (g/dL)	3.1 (2.6–3.3)	3.0 (2.9–3.5)	3.2 (2.6–3.6)	2.4–3.6	.33
Globulin (g/dL)	3.2 (2.9–3.7)	3.5 (3.1–4.0)	3.2 (2.9–3.7)	1.7–3.8	.60
ALT (U/L)[b]	82 (51–182)	99 (43–137)	104 (66–191)	10–130	.55
ALP (U/L)[b]	834 (314–1818)	609 (283–989)	859 (297–1352)	24–147	.83
GGT (U/L)[b]	16 (10–34)	18 (11–28)	16 (12–35)	0–25	.54
Total bilirubin (mg/dL)[b]	0.4 (0.2–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.0–0.8	.72
Sodium (mmol/L)	139 (132–146)	143 (139–147)	138 (131–142)	139–147	.18
Potassium (mmol/L)	4.0 (3.4–4.6)	4.0 (3.4–4.4)	3.6 (2.8–4.6)	3.3–4.6	.20
Chloride (mmol/L)	104 (96–110)	108 (102–115)	104 (98–110)	107–116	.29
Total carbon dioxide (mmol/L)	14[a] (9–17)	17[b] (14–20)	13[a] (9–16)	21–28	.020
Anion gap (mmol/L)	26 (20–32)	22 (19–27)	25 (19–30)		.20

[a]Based on 1-way ANOVA comparing the three groups. Medians without superscripts in common were significantly different ($P < .05$) based on posthoc pairwise comparisons with Bonferroni correction of *P* values.
[b]Variable transformed prior to statistical analysis.

Table 3. Coagulation results in dogs with diabetic ketoacidosis (DKA).

Variable	Untested (n = 57)	cPLI negative (n = 17)	cPLI positive (n = 45)	*P* value[a]
PT[b]	7.1 (6.5–7.7)	6.5 (6.0–7.1)	7.4 (6.9–8.0)	.20
PTT[b]	9.7 (9.1–13.9)	9.4 (9.2–10.9)	11.0 (8.6–12.6)	.70
Fibrinogen[b]	516 (255–978)	574 (563–574)	574 (480–1100)	.68
ATIII	89 (69–123)	136 (57–176)	120 (88–138)	.14
D-dimers[b]	517 (330–1551)	332 (261–391)	768 (399–1514)	.27
Venous pH	7.28 (7.22–7.34)	7.40 (7.30–7.45)	7.34 (7.27–7.40)	.068
Lactate[b]	1.5 (1.1–2.7)	1.9 (1.2–2.3)	1.8 (0.9–2.5)	.67
HCO3	12 (9–15)	16 (11–18)	13 (10–15)	.26
iCA	4.7 (4.4–5.0)	4.8 (4.5–5.0)	4.7 (4.3–4.9)	.82

[a]Based on 1-way ANOVA comparing the three groups.
[b]Variable transformed prior to statistical analysis.

Table 4. Urinalysis results for dogs with diabetic ketoacidosis (DKA).

Variable	Untested (n = 57)	cPLI negative (n = 17)	cPLI positive (n = 45)	*P* value
Categorical[a]				
Protein	0.88 (0.76–0.95)	0.88 (0.66–0.98)	0.93 (0.83–0.98)	.62
Casts	0.36 (0.23–0.51)	0.18 (0.05–0.41)	0.44 (0.30–0.59)	.15
WBC	0.67 (0.53–0.79)	0.65 (0.40–0.84)	0.80 (0.66–0.90)	.28
RBC	0.52 (0.38–0.66)	0.47 (0.25–0.70)	0.69 (0.54–0.81)	.16
Bacteria	0.13 (0.05–0.24)	0.06 (0–0.26)	0.16 (0.07–0.28)	.59
Quantitative[b]				
USG	1.028 (1.021–1.038)	1.026 (1.020–1.035)	1.023 (1.018–1.032)	.059
Urine pH[c]	6.0 (6.0–6.5)	6.0 (5.5–6.5)	6.0 (6.0–6.5)	.64

[a]Categorical data presented as the proportion and 95% confidence interval. *P* value calculated using chi-square tests comparing proportions between the three groups.
[b]Quantitative data presented as the median and interquartile range. *P* value calculated using 1-way ANOVA comparing the three groups.
[c]Variable transformed prior to statistical analysis.

histopathology as the gold standard, a PLI result greater than twice the upper limit of the reference range has a sensitivity of 67–93%.[11,16,17,j] and is likely to identify more dogs with pancreatitis than AUS, with a reported sensitivity of 65–70% for the diagnosis of pancreatitis.[10,11]

We did not identify any significant differences in demographics between the three groups of dogs, although relatively small numbers might have impacted these findings. Few differences were noted in hematologic and biochemical variables between the three groups. The median band neutrophil count was higher for the PLI_{pos} group than the PLI_{neg} group, consistent with a systemic inflammatory effect. In addition, the metabolic acidosis was more severe in the PLI_{pos} group compared to the PLI_{neg} group. This might reflect higher rates of ketosis secondary to insulin resistance from pancreatic injury, greater bicarbonate loss through emesis, or more severe lactic acidosis secondary to compromised perfusion.

Acute pancreatitis is a cause of acute kidney injury, probably because of compromised perfusion and endothelial damage.[18] Dogs in the PLI_{pos} group were not significantly more azotemic or more likely to have urine casts compared to dogs in the PLI_{neg} or PLI_{na} groups. This could have been influenced by the administration of fluid therapy before arrival at our institution. Biochemical evidence of pancreatic injury was not associated with significant differences in coagulation variables.

Our study found only fair agreement between AUS and PLI for the diagnosis of pancreatic injury ($\kappa = 0.26$). This agrees with the findings of a recent study, where despite excellent agreement between two lipase assays for pancreatic injury (DGGR lipase assay and PLI, $\kappa = 0.80$), only fair agreement ($\kappa = 0.25$) was found between both lipase assays and AUS.[19] There are several potential explanations for limited agreement between AUS and PLI in our study population. First, AUS can have limited sensitivity in dogs with mild or chronic disease, particularly if changes in echogenicity are modest and the adjacent structures are unremarkable. These dogs can have a PLI indicative of pancreatic injury but be classified as 'normal' based on AUS. Alternatively, ultrasonographic abnormalities of the pancreas and adjacent structures may persist despite resolution of acinar injury. These individuals may have a PLI within the reference range despite a diagnosis of 'pancreatitis' based on AUS. Although there is limited information regarding the clearance of PLI from the vascular space, serum half-life appears to be approximately 105 minutes.[k] Theoretically, serum PLI could therefore return to the reference interval as early as 24 hours after cessation of pancreatic acinar cell damage despite changes consistent with pancreatitis on AUS.

Currently, there is no consensus regarding optimal noninvasive testing for pancreatitis in dogs and many clinicians rely on both AUS and PLI results. Although not routinely utilized in the clinical setting, computed tomographic angiography appears superior to AUS in its ability to visualize overt and subtle pancreatic abnormalities, identify potential complications such as portal vein thrombi, and provide prognostic information.[20]

There was no difference in hospitalization period between the PLI_{pos} and the PLI_{neg} group (4 days), which might be explained by the lack of power due to the relatively small numbers of dogs in each group. Studies with larger numbers of dogs would be needed to determine if the duration of hospitalization for dogs with DKA is affected by the PLI result.

Due to the small sample size in the PLI_{neg} group, short-term outcomes of death or euthanasia versus discharge were compared between the PLI_{pos} and $PLI_{na} + PLI_{neg}$ groups. Dogs in the $PLI_{na} + PLI_{neg}$ group were more likely to be euthanized but not die; however, this is likely related to the large number of dogs in the PLI_{na} group that were euthanized within 6 hours of admission. Reasons for this could not be reliably established, but it is likely a reflection of an owner reluctance to treat rather than the severity of dog compromise. This presumption is supported by the overall similarity of the PLI_{na} dogs to the other two groups with respect to biochemical and hematologic parameters. Therefore, meaningful conclusions about the impact of PLI results on short-term outcome cannot be made on the basis of these data.

There were several limitations to this study. Primarily, we were not able to compare PLI results to those of histopathology, which is the gold standard for the diagnosis of pancreatic injury. It is possible, but unlikely, that some of the dogs included in this study had a neoplastic cause for the abnormal PLI results. In addition, PLI was not measured in all dogs, which may have biased our findings. It is possible that clinicians chose to measure PLI in more overtly compromised dogss or those with obvious abdominal pain. Consequently, our prevalence of 73% might be an overestimation of the likelihood of pancreatic injury in dogs with DKA. Also, two different PLI assays were used to evaluate dogs for pancreatic injury over the time frame included in the study. Although reference ranges were appropriately established for both assays, sensitivity and specificity might be different. Furthermore, in some cases, a substantial period of time elapsed between the onset of clinical signs consistent with pancreatic injury and collection of blood for measurement of PLI. This might have impacted our results regarding the prevalence of pancreatic injury and contributed to the limited agreement between AUS and PLI results. Some dogs received treatment at other hospitals prior to presentation, which might have also influenced biochemical findings. Ideally, the same radiologist would have performed every examination; this was not the case and numerous individuals imaged these dogs. The radiologists might also have been biased by information provided by the attending clinician regarding the status of the dog and the clinical index of suspicion for concurrent pancreatitis. Conclusions about the impact of an abnormal PLI result on outcome and duration of hospitalization were limited by the small sample size in the PLI_{neg} group.

Based on our findings, pancreatic injury is a common concurrent disease in dogs with DKA, affecting about 70% of dogs. However, biochemical evidence of pancreatic injury did not affect outcome or significantly prolong the duration of hospitalization. Longitudinal studies with larger dog numbers are needed to determine the full impact of concurrent pancreatic injury in dogs with DKA, including risk of recurrence, insulin responsiveness, long-term survival, and overall quality of life.

Footnotes

[a] Stat Profile© pHOx Ultra, Nova Biomedical, Waltham, MA
[b] Chemistry analyzer, Vitros® 4600, Ortho-Clinical Diagnostics, Rochester, NY
[c] Multistix® 10 SG, Siemens Healthcare, Malvern, PA
[d] Spec cPL®, Idexx Laboratories, Westbrook, ME
[e] Hematology analyzer, Cell-Dyn 3700, Abbott Laboratories, Ramsey, MN
[f] Coagulation analyzer, IL ACL 9000, Instrumentation Laboratory, Bedford MA
[g] Acuson S2000 Ultrasound System, Siemens Healthcare, Malvern, PA
[h] MINITAN Statistical Software, Release 13.32, Minitab Inc., State College, PA
[i] IBM SPSS Statistics Version 23, International Business Machines Corp., Armonk, NY
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[k] Dossin O, Rick M, Ridge TK, Williams D, Grützner N, et al. Pharmacokinetics of pancreatic lipase in healthy dogs. Proceedings of the 21st ECVIM-CA Congress, Sevilla, Spain

Acknowledgment

Conflict of Interest Declaration: Dr. Joerg Steiner is Director of the GI Laboratory at Texas A&M University, which offers the PLI test on a commercial basis.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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