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. Prolonged absolute or relative insulin deficiency results in accelerated lipolysis, hypertriglyceridemia, and ketone body production. When ketone production exceeds peripheral utilization, the associated hydrogen ions overwhelm the body’s buffering systems. 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. Concurrent disorders, such as pancreatitis, urinary tract infection, hyperadrenocorticism, and neoplasia are often reported. These conditions can decrease insulin sensitivity through the release of counterregulatory hormones and inflammatory cytokines.

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. Twenty percent of people with DKA develop severe or life-threatening pancreatitis requiring prompt diagnosis and aggressive management. 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.
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). Acute pancreatitis is the most prevalent concurrent disorder in dogs with DKA, and occurs in 40% of dogs with DKA. Although it did not appear to impact outcome, assessed as survival to discharge or euthanasia, dogs with pancreatitis required longer periods of hospitalization. The diagnosis of pancreatitis was based on AUS (38%; 48/127 dogs) or necropsy findings (5%; 6/127 dogs) and likely underestimated the true prevalence of concurrent pancreatitis, as AUS has only modest diagnostic sensitivity for this disease.

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 or 200–135 mmol/L), metabolic acidosis (total carbon dioxide ≤20 mmol/L; reference interval: 21–28 mmol/L), and ketonuria (based on urine dipstick analysis) within 6 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. Additional supportive findings included corrugation of the duodenum, a distended, hypotonic stomach or duodenum, peripancreatic effusion, or extrahepatic bile duct obstruction. 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. Data violating the normality assumption were transformed before statistical analysis using the natural logarithm or by ranking 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 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 (PLIpos 7%, PLIneg 5%, PLIna 9%) and mixed-breed dog (PLIpos 13%, PLIneg 12%, PLIna 19%). Five miniature schnauzers were present in the study population, with four of them being in the PLIpos group; the fifth dog was in the PLIna group.

Results of CBCs (Table 1), biochemistry profiles (Table 2), coagulation profiles (Table 3), and urinalyses (Table 4) are provided for dogs in the PLIpos, PLIneg, and PLIna groups. The median band neutrophil count was significantly higher in the PLIpos group compared to the PLIneg group (P = .001). The median serum glucose concentration was significantly higher in the PLIna group compared to the PLIneg group (P = .03), and the median total carbon dioxide was significantly lower in the PLIpos group compared to the PLIneg group (P = .03), and the median band neutrophil count was significantly higher in the PLIpos group compared to the PLIneg 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 PLIpos group and 13/17 in the PLIneg group). Finding on AUS for the PLIpos 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 PLIneg 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 PLIpos group and 47% (8/17) of dogs in the PLIneg group. Overall agreement between AUS and PLI was fair (κ = 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 PLIna 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 PLIpos dogs (6 days, range 4–7 days) was not significantly longer than for the PLIneg group (4 days, range 3–6 days).

Eleven dogs in the PLIpos group did not survive to discharge (24%; 2 died, 9 euthanized), and 2 dogs in the PLIneg group did not survive (12%; both died). Over half (30/57; 53%) of the PLIna 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 PLIna group were significantly more likely to be euthanized (P = .03), but were not more likely to die (P = .71) compared to dogs in the PLIpos 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. Despite a relatively high prevalence, no clinicopathologic variables aside from band neutrophil count and total carbon dioxide were significantly different between PLIpos and PLIneg 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. 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 valuea |
|----------|------------------|-----------------------|------------------------|-------------------|----------|
| WBC (10⁴ 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 (10⁴ 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 (0–521) | 0 (0–0) | 206 (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 (530–2593) | 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 (10⁴ 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 (10⁶/L) | 6.07 (5.27–6.54) | 5.98 (5.62–7.67) | 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 |

*aBased 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.

*bVariable 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 valuea |
|-------------------|------------------|------------------------|-----------------------|--------------------|----------|
| Glucose (mg/dL)b  | 490a (374–609)   | 363b (294–473)         | 431b (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° (9–17) | 17° (14–20)           | 13° (9–16)            | 21–28              | .020     |
| Anion gap (mmol/L) | 26 (20–32)     | 22 (19–27)             | 25 (19–30)            | 20                  |         |

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

| Variable          | Untested (n = 57) | cPLI negative (n = 17) | cPLI positive (n = 45) | P valuea |
|-------------------|------------------|------------------------|-----------------------|----------|
| PTb               | 7.1 (6.5–7.7)    | 6.5 (6.0–7.1)          | 7.4 (6.9–8.0)         | .20      |
| PTTb              | 9.7 (9.1–13.9)   | 9.4 (9.2–10.9)         | 11.0 (8.6–12.6)       | .70      |
| Fibrinogenb       | 516 (255–978)    | 574 (563–574)          | 574 (480–1100)        | .68      |
| ATIII             | 89 (69–123)      | 136 (57–176)           | 120 (88–138)          | .14      |
| D-dimersb         | 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     |
| Lactateb          | 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      |

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

| Variable          | Untested (n = 57) | cPLI negative (n = 17) | cPLI positive (n = 45) | P valuea |
|-------------------|------------------|------------------------|-----------------------|----------|
| Categoricalb      |                  |                        |                       |          |
| 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      |
| Quantitativeb     |                  |                        |                       |          |
| USG               | 1.028 (1.021–1.038)| 1.026 (1.020–1.035)   | 1.023 (1.018–1.032)   | .059     |
| Urine pHb         | 6.0 (6.0–6.5)    | 6.0 (5.5–6.5)          | 6.0 (6.0–6.5)         | .64      |

bBased on 1-way ANOVA comparing the three groups.
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%.10,11,16,17,3 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 PLIpos group than the PLIneg group, consistent with a systemic inflammatory effect. In addition, the metabolic acidosis was more severe in the PLIpos group compared to the PLIneg 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. Dogs in the PLIpos group were not significantly more azotemic or more likely to have urine casts compared to dogs in the PLIneg or PLIna 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 glucose or electrolyte values between the groups.

Our study found only fair agreement between AUS and PLI for the diagnosis of pancreatic injury (κ = 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, κ = 0.80), only fair agreement (κ = 0.25) was found between both lipase assays and AUS. The absence of 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 show relatively normal results of histopathology, which is the gold standard for the diagnosis of pancreatic injury. Furthermore, 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. 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 PLIneg group.

Based on our findings, pancreatic injury is a common concurrent disease in dogs with DKA, affecting about 76% 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
j Steiner JM, Brousard J, Mansfield CS, Gumminger SR, Williams DA. Serum canine pancreatic lipase immunoreactivity (cPL) concentrations in dogs with spontaneous pancreatitis. J Vet Intern Med 2001;5:274
k Dossin O, Rick M, Ridge TK, Williams D, Grützner N, et al. Pharmacoceutics of pancreatic lipase in healthy dogs. Proceedings of the 21st ECVIM-CA Congress, Sevilla, Spain

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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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