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Beta-hydroxybutyrate Concentrations in Dogs with Acute Pancreatitis and Without Diabetes Mellitus

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Background: β-hydroxybutyrate (BOHB) concentrations have not been quantified in dogs with acute pancreatitis (AP).

Objective: The aim of this study was to investigate BOHB concentrations in dogs with AP.

Animals: A total of 154 client-owned dogs without DM.

Methods: Prospective clinical study. Dogs were enrolled into 1 of 3 groups: AP, sick without an AP diagnosis, or fasted. Dogs were diagnosed with AP (44) if they had vomiting or anorexia, and either ultrasonographic findings consistent with AP or increased pancreatic lipase. Sick dogs without AP (68) had vomiting or anorexia but a diagnosis of AP was either not suspected or was excluded based on ultrasonographic findings or a normal pancreatic lipase. Dogs without anorexia or vomiting that were fasted for over 10 hours for a procedure were also enrolled (42). BOHB was measured on whole blood with a portable ketone meter. The Kruskal-Wallis test was performed to compare BOHB in the 3 groups. Pair-wise comparisons were performed using the Mann-Whitney test and Bonferroni corrected *P*-values are reported.

Results: Median BOHB concentration was significantly higher in dogs with AP (0.3 mmol/L, range 0–2.9 mmol/L) compared to sick dogs without AP (0.20 mmol/L, range 0–0.9 mmol/L, $P = .007$) and fasted dogs (0.1 mmol/L, range 0–0.4 mmol/L, $P = .0001$). Median BOHB concentration was significantly higher in sick dogs without AP compared to fasted dogs ($P = .0002$).

Conclusions and clinical importance: In dogs without DM, BOHB is significantly higher in dogs with AP compared to other dogs. The diagnostic utility of this finding remains to be investigated.

Key words: Anorexia; Diabetic ketoacidosis; Ketone; Vomiting.

Diabetic ketoacidosis (DKA) is a life threatening diabetic complication characterized by excess β-hydroxybutyrate (BOHB) production. Many dogs with DKA also have acute pancreatitis (AP), and in humans, AP is characterized by excess BOHB production.[1–3] If dogs with AP have excess BOHB production, it may be difficult to determine the cause of increased BOHB concentration in dogs that have concurrent DKA and AP.

The pathogenesis of ketonemia in humans with AP is incompletely understood. One explanation is that excess alcohol consumption can cause both ketonemia and AP. However, ketonemia occurs in humans with AP that have not consumed excess alcohol.[2,3] Another explanation is that markedly increased pancreatic lipase (PL) results in peripancreatic or systemic lipolysis, which leads to ketone production.[2] Anorexia, vomiting and dehydration, all common clinical sign in AP, can also contribute to ketone synthesis.[3] Finally, in human beings without DM, AP is associated with insulin resistance, which can promote lipolysis and ketonemia.[4] Increased BOHB concentrations in humans occur in non-pancreatic disorders in association with starvation (especially in pregnancy), persistent hypoglycemia, hyperthyroidism, low carbohydrate and high protein diets, toxicities (salicylate, isopropyl alcohol, isoniazid), inborn errors of metabolism and sepsis.[5–9] In dogs, BOHB concentrations are increased with DKA, diabetic ketosis without acidosis, well-regulated DM, inflammatory bowel disease and in dogs fed diets with high diacylglycerol or medium chain triacylglyceride.[10–16]

Abbreviations:

BOHB	beta-hydroxybutyrate
AP	acute pancreatitis
PL	pancreatic lipase
PLI	pancreatic lipase immunoreactivity
DM	diabetes mellitus
SD	standard deviation

A total of 41% of dogs with DKA have concurrent AP.[1] Therefore, an investigation into whether AP alone can cause increased BOHB concentrations is of interest. If AP causes an increase in BOHB, then dogs with DM and concurrent AP could be misdiagnosed with diabetic ketosis or DKA when the reason for the ketosis is actually AP.

Point-of-care ketone meters are inexpensive and are quick and easy to use. Their use has been validated in dogs with DKA, and whole blood BOHB concentrations measured with a point-of-care ketone meter have been shown to be well correlated with measurements obtained with a biochemical analyzer.[10–12]

The goal of this study was therefore to determine whether dogs with AP and without diabetes mellitus

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(DM) have higher point-of-care ketone meter measured BOHB concentrations compared to other sick or fasted dogs without DM.

Materials and Methods

A prospective clinical study was performed. Dogs with anorexia or vomiting were enrolled in the study from the population of client-owned dogs examined at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania between July 2013 and November 2014. Dogs were classified into 1 of 3 study groups. The first group comprised dogs with anorexia or vomiting and a diagnosis of AP. The second group included dogs with anorexia or vomiting in which a diagnosis of AP was excluded or not suspected by the attending clinician. The third study group included dogs that were fasted for at least 10 hours and had no anorexia or vomiting. These dogs were fasted for the purpose of performing a diagnostic test, surgery or dental care.

Inclusion criteria for dogs that were classified as having AP were clinical signs consistent with the disease (anorexia or vomiting), and ultrasonographic findings suggestive of AP or high PL measured either as an abnormal SNAP cPL or as pancreatic lipase immunoreactivity (PLI) >400 mcg/L.[a,b]

Ultrasonographic reports finalized by a radiologist who is board certified by the American College of Veterinary Radiology, were reviewed and pancreatic ultrasonographic findings were recorded. Ultrasonographic findings were defined as suggestive of AP if dogs had at least 2 of the 4 following ultrasonographic changes: enlarged pancreas, heteroechoic pancreas, hypoechoic pancreas or hyperechoic peripancreatic mesentery.

Inclusion criteria for enrolment into the sick group of dogs without a diagnosis of AP were clinical signs of anorexia or vomiting. Dogs with anorexia or vomiting were chosen for this comparison group, because their clinical signs are similar to those exhibited by dogs with AP. In addition, a diagnosis of AP was either not suspected by the attending clinician or excluded based on PL measurement or abdominal ultrasound findings. PL measurements were defined as inconsistent with a diagnosis of AP, if SNAP cPL was normal or if PLI was <200 mcg/L.[a,b] Ultrasonographic findings were defined as inconsistent with a diagnosis of AP if dogs had only one or none of the following 4 ultrasonographic changes: enlarged pancreas, heteroechoic pancreas, hypoechoic pancreas or hyperechoic peripancreatic mesentery. The decision whether to measure PL or have an abdominal ultrasound performed was made by the attending clinician and not by the authors. The final medical record diagnoses of sick dogs with vomiting or anorexia and no diagnosis of AP were recorded. Dogs were enrolled into the fasted group if they were fasted for at least 10 hours and had no anorexia or vomiting.

Dogs were excluded from the study if they were <1 year old or had DM. Dogs were also excluded if they had incidental ultrasonographic findings supportive of a diagnosis of AP, but did not have clinical signs suggestive of the disease. Finally, dogs were excluded if they were suspected of having AP, but PL was not measured and an abdominal ultrasound was not performed.

A drop of whole venous blood, from a blood sample collected by direct venipuncture for the purpose of other diagnostic testing, was immediately used to measure BOHB using a point-of-care ketone meter.[c] Dogs were not subjected to venipuncture solely for the purpose of this study, and blood was used only if it was being drawn for other diagnostic testing. The study protocol was approved by the University of Pennsylvania Institutional Animal Care and Use Committee, and owners gave consent for venipuncture for the purpose of diagnostic testing suggested by the attending clinician. The point-of-care ketone meter was operated in accordance with the manufacturer's recommendations except that venous rather than capillary blood was used.[17] The point-of-care ketone meter was calibrated in accordance with the manufacturer's instructions with manufacturer-provided control solutions at the onset of the study and each time a new box of 10 test strips was opened.[17]

Additional data including history, physical examination findings, and laboratory and imaging test results were recorded when available in the medical record. Duration of hospitalization, the numbers of hours a dog had anorexia or fasting at the time BOHB was measured, and outcome (survival to discharge from the hospital versus death) was also noted.

A power calculation was performed based on data reported in another study which established a reference range of 0.02 to 0.15 mmol/L for serum BOHB based on measurements from 50 healthy dogs.[10] Using this reference range and assuming a normal distribution in which the reference range is two standard deviations (SD) above and below the mean, it was calculated that mean serum BOHB concentration in healthy dogs is 0.085 mmol/L and the SD is 0.032 mmol/L.[10] It was also assumed that the SD of the BOHB concentrations measured on whole blood by the point-of-care ketone meter would be similar to the SD of the BOHB concentrations measured on serum by a biochemical analyzer.[10] Using these numbers, the sample size required to detect a difference of at least 0.1 mmol/L between BOHB concentrations measured in the 3 groups of dogs was calculated. The smallest measurable unit in the ketone meter used is 0.1 mmol/L. The calculation with a power of 0.8 and type I error rate of 0.05, resulted in a required sample size of 25 blood samples in each group. However, additional samples from eligible dogs were analyzed as they became available until the end of the allocated research time.

Whole blood venous BOHB concentrations were not normally distributed as determined by the Shapiro-Wilks test, so the nonparametric Kruskal-Wallis test was used for the initial comparison of BOHB concentrations in the 3 groups, and the Mann-Whitney test was performed for follow-up pair-wise comparisons if the *P*-value of the Kruskal-Wallis test was <0.05. Each *P*-value was multiplied by 3 to get the Bonferroni corrected *P*-value and a *P*-value <.05 was considered significant.

Spearman's correlation was used to assess if there was an association between BOHB concentration and duration of hospitalization or hours fasted in all 154 study dogs. For dogs with AP and sick dogs without a diagnosis of AP, Spearman's correlation was also used to assess associations between BOHB and total white blood cell count, serum glucose, cholesterol, or lactate concentrations, venous pH, body temperature, an overweight or obese body condition, and outcome. Several clinicopathologic parameters were compared between the 3 groups using the Kruskal-Wallis test and pair-wise comparisons using the Mann-Whitney test for groups that were significantly different. These variables included age, body temperature, duration of hospitalization, total white blood cell count, alkaline phosphatase activity, venous pH, and concentrations of serum glucose, alanine amino transferase, total bilirubin, cholesterol, and lactate. Fisher's exact test was used to assess if there was a significant difference in outcome between the 3 groups. All statistical analyses were performed using a statistical software package.[d]

Results

One hundred and fifty-four dogs were enrolled in the study: 68 sick dogs without a diagnosis of AP, 44 dogs with AP, and 42 fasted dogs. Median BOHB concentration was significantly higher in dogs with AP (0.3 mmol/L, range 0–2.9 mmol/L) compared to sick dogs without a diagnosis of AP (0.2 mmol/L, range 0–0.9 mmol/L, $P = .007$) and compared to fasted dogs (0.1 mmol/L, range 0–0.4 mmol/L $P = .0001$, Fig 1). Median BOHB concentration was also significantly higher in sick dogs without a diagnosis of AP compared to fasted dogs ($P = .0002$). When 154 study dogs were analyzed

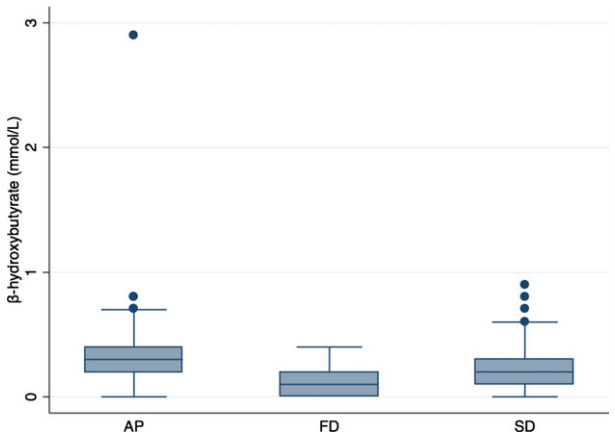

Fig 1. Box and Whisker plot of Beta-hydroxybutyrate (BOHB) concentrations in dogs with acute pancreatitis (AP), sick dogs without AP (SD), and fasted dogs (FD). The line within the box represents the median, the box represents the interquartile range, whiskers represent the most extreme values within 1.5 of the nearer quartile, and the single points represents an outlier. Median BOHB concentration was significantly higher in dogs with AP compared to sick dogs without a diagnosis of AP ($P = .007$) and compared to fasted dogs ($P = .0001$). Median BOHB concentration was also significantly higher in sick dogs without a diagnosis of AP compared to fasted dogs ($P = .0002$).

together, a weak but significant association was detected between a longer duration of hospitalization and increased BOHB concentration ($P = .0044$, $r = 0.22$).

The highest concentration of BOHB measured in the fasted group was 0.4 mmol/L. Ten dogs (23%) with a diagnosis of AP had a BOHB concentration >0.4 mmol/L, while only 5 dogs (7%) of sick dogs without a diagnosis of AP had a BOHB concentration >0.4 mmol/L. Only one study dog had a BOHB concentration >2.0 mmol/L, and this dog was in the AP group (BOHB concentration was 2.9 mmol/L).

No significant associations were found between BOHB concentrations and hours fasted, overweight or obese body condition, body temperature, or outcome. White blood cell count, venous pH, and concentrations of glucose, lactate, and cholesterol were also not associated with BOHB concentration in dogs with AP or sick dogs without a diagnosis of AP. However, in comparison to fasted dogs, dogs with AP and sick dogs without a diagnosis of AP had significantly higher body temperature, significantly higher white blood cell counts, significantly longer duration of hospitalization, significantly worse outcome, significantly higher alanine aminotransferase activity, significantly higher total bilirubin concentration, and significantly higher alkaline phosphatase activity compared to fasted dogs (Tables 1 and 2). None of these values were significantly different when comparing dogs with AP to sick dogs without a diagnosis of AP. However, dogs with AP were significantly older than sick dogs without a diagnosis of AP (Table 1). Venous pH and concentrations of lactate, cholesterol and glucose were not significantly different between any of the groups of dogs.

The diagnosis of AP was based on clinical signs and ultrasound findings in 24 of 44 dogs (54%), clinical signs and abnormal SNAP cPL in 10 of 44 dogs (23%), clinical signs, ultrasound findings, and PLI of 1000 mcg/L in 4 of 44 dogs (9%), clinical signs, ultrasound findings, and abnormal SNAP cPL in 3 of 44 dogs (7%), and clinical signs with PLI>400 mcg/L in 3 of 44 dogs (7%). In 3 dogs with PLI>400 mcg/L, PLI concentrations were 493 mcg/L, 792 mcg/L, and 1000 mcg/L.

Two dogs in which BOHB was measured were excluded from the study. Both were excluded because they had incidental ultrasonographic findings supportive of a diagnosis of AP but did not have clinical signs suggestive of the disease. BOHB concentrations in these dogs were 0.2 mmol/L and 0.3 mmol/L and one of these dogs had pancreatic neoplasia.

Discussion

Median venous blood BOHB concentration was significantly higher in dogs with AP compared to sick dogs without a diagnosis of AP and fasted dogs without vomiting or anorexia. However, from a clinical perspective,

Table 1. Age, hours of anorexia or fasting, overweight or obese body condition, body temperature, duration of hospitalization and survival to discharge in dogs with acute pancreatitis (AP), sick dogs without a diagnosis of AP, and fasted dogs.

	Age (years, median range)	Hours of anorexia	Overweight or obese body condition	Body temperature (°F [°C], median, range)	Duration of hospitalization (days, median range)	Survival to discharge
Dogs with AP (44)	10 (1.4–15.2)	24 (5–120)	15 (34%)	101.6 [38.7] 98.6–103.9 [37.0–39.9]	2.5 (0–10)	36 (82%)
Sick dogs without a diagnosis of AP (68)	7.3 (1.2–18.5)	22 (6–120)	21 (31%)	101.4 [38.6] 97.6–105 [36.4–40.6]	2.0 (0–10)	61 (90%)
Fasted dogs (42)	9 (1–15.2)	14 (10–48)	11 (26%)	101.0 [38.3] 98.6–102.8 [37–39.3]	1.0 (0–7)	42 (100%)
P-value*	.041 .0091[a]	NA	.679	.019 .012[b] .009[c]	.0001 <.0001[b] <.0001[c]	.008 .006[b] .043[c]

[a]Significantly different between dogs with AP and sick dogs without a diagnosis of AP.
[b]Significantly different between dogs with AP and fasted dogs.
[c]Significantly different between sick dogs without a diagnosis of AP and fasted dogs.
*P-value <.05 was considered significant

Table 2. Comparison of selected clinicopathologic abnormalities in dogs with acute pancreatitis (AP), sick dogs without a diagnosis of AP, and fasted dogs.

	AP (44 dogs)		Sick without AP (68 dogs)		Fasted (42 dogs)			
Variable	Median	Range	Median	Range	Median	Range	*P*-value*	Reference range
Serum Glucose (mg/dL)	89 (n = 44)	45–154	90 (n = 68)	49–141	94 (n = 42)	75–134	.3	67–112
Cholesterol (mg/dL)	233.5 (n = 36)	102–532	202.5 (n = 48)	65–461	219 (n = 33)	89–451	.3	128–317
Total Bilirubin (mg/dL)	0.4 (n = 39)	.1–22.1	0.3 (n = 54)	0.1–70.3	0.2 (n = 35)	0.1–0.8	.004 .05[a] .0007[b] .001[c]	0.1–0.5
Alanine aminotransferase (U/L)	75.5 (n = 42)	7–4352	75 (n = 56)	13–1616	43 (n = 37)	12–374	.02 .8[a] .03[b] .005[c]	16–91
Alkaline phosphatase (U/L)	251 (n = 42)	22–4248	147 (n = 54)	28–8414	68 (n = 37)	5–1187	.0001 .08[a] <.0001[b] .001[c]	20–155
Venous pH	7.4145 (n = 38)	7.2–7.645	7.402 (n = 49)	7.183–7.516	NA	NA	0.7	7.35–7.45
Lactate (mmol/L)	1.7 (n = 35)	0.6–3.8	1.4 (n = 41)	0.2–4.8	NA	NA	0.4	0–1.5
White blood cells ($\times 10^3$/uL)	15.4 (n = 39)	4.88–34.3	14.4 (n = 54)	3.65–73.9	9.385 (n = 38)	5.44–32.7	.0001 .6[a] .0001[b] <.0001[c]	5.3–19.8

*The upper most *P*-value represents the value obtained when comparing all 3 groups with the Kruskal-Wallis test. The following 3 *P*-values (a, b, c) represent the Bonferroni corrected Mann-Whitney test for pair-wise comparisons between each of the two groups. A *P*-value <.05 was considered significant.

[a]Dogs with AP compared to sick dogs without a diagnosis of AP.

[b]Dogs with AP compared to fasted dogs.

[c]Sick dogs without a diagnosis of AP compared to fasted dogs.

the difference in median BOHB concentration between the 3 groups of dogs was small (0.1 mmol/L). It is generally accepted that a BOHB concentration greater than or equal to 2 mmol/L is consistent with a diagnosis of DKA in dogs that also have hyperglycemia and acidemia.[18,19] Therefore, an AP related increase of 0.1 mmol/L in the concentration of BOHB is unlikely to contribute to a false diagnosis of DKA in a dog with DM and AP. However, 10 dogs with AP (23%) had a BOHB concentration >0.4 mmol/L, while only 5 sick dogs without a diagnosis of AP (7%) had a BOHB concentration >0.4 mmol/L, and none of the fasted dogs had a BOHB concentration >0.4 mmol/L. While some dogs with AP can have a high enough BOHB concentration to confound the diagnosis of diabetic ketosis in a dog with concurrent DM it is unlikely that an increase in BOHB concentration alone would prompt a false diagnosis of DKA. In order for a diagnosis of DKA to be established, venous pH must be low. However, median venous pH was normal in dogs with AP and was not significantly different than median venous pH in dogs without a diagnosis of AP. Future studies in dogs with DKA or diabetic ketosis with and without concurrent AP are indicated to further investigate BOHB concentrations in dogs with these comorbidities.

A weak association between BOHB concentration and duration of hospitalization was identified in this study, but the causality of this association is not known. It is possible that prolonged hospitalization reflects prolonged anorexia, which leads to an increase in BOHB concentration. Conversely, it is possible that dogs with higher BOHB concentration had a more severe illness that resulted in prolonged hospitalization. Future larger studies focusing on dogs with AP may be able to determine if there is an association between the severity of AP and BOHB concentration.

The point-of-care ketone meter was chosen for this study because it is quick, easy, inexpensive, and convenient, and has been shown to correlate well with the gold standard biochemical analyzer in dogs.[11,20] The meter works by facilitating an enzymatic reaction in which BOHB is the substrate, and an electric current proportional to BOHB concentration is generated as BOHB is metabolized.[11]

The main limitation of this study is that the diagnosis and exclusion of AP were not definitive. Ideally, all dogs diagnosed with AP would have had clinical signs consistent with the disease, and ultrasonographic as well as enzymatic evidence of AP. However, most of the dogs diagnosed with AP had clinical signs consistent with the disease, and either ultrasonographic findings consistent with a diagnosis of AP or increased PL. Therefore, some dogs could have been incorrectly diagnosed with AP. While both the SNAP cPL and PLI can be useful for the diagnosis of AP in dogs, some studies have reported false-positive and false-negative test results.[21–25] False-

positive PL concentrations have been reported in up to 40% of dogs examined with acute abdominal disease.[24] A 55% false-positive rate of SNAP cPL has also been reported in dogs with hyperadrenocorticism and without clinical signs of pancreatitis.[25] Additionally, in the group of sick dogs without a diagnosis of AP, AP was not definitively excluded in all of the dogs. If the attending clinician did not suspect AP, diagnostics excluding this diagnosis were not pursued. Therefore, dogs with AP could have been misclassified as not having AP. Allocation of dogs to the incorrect group could have decreased the difference in BOHB concentration between dogs with AP and sick dogs without AP.

It is concluded that BOHB concentration is significantly higher in dogs with AP, compared to sick dogs without a diagnosis of AP and fasted dogs. However, the magnitude of this difference is small in most dogs. Therefore, the increase in BOHB related to AP is unlikely to confound the diagnosis of DKA or diabetic ketosis in most dogs. The clinical significance of BOHB concentrations in other inflammatory diseases and in dogs with concurrent AP and DKA, or diabetic ketosis remains to be studied.

Footnotes

[a] SNAP cPL; IDEXX laboratories, Westbrook, ME
[b] Spec cPL; IDEXX laboratories
[c] Precision Xtra; Abbot Laboratories, Abbott Park, IL
[d] Stata 11.0 for Windows; Stata Corporation, College Station, TX

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

References

1. Hume DZ, Drobatz KJ, Hess RS. Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993-2003). J Vet Intern Med 2006;20:547–555.

2. Kibadi UM. Pancreatic ketoacidosis: ketonemia associated with acute pancreatitis. Postgrad Med J 1995;71:32–52.

3. Villasenor A, Kinross JM, Li JV, et al. 1-NMR global metabolic phenotyping of acute pancreatitis in the emergency unit. J Proteome Res 2014;13:5362–5375.

4. Wu D, Xu Y, Zeng Y, Wang X. Endocrine pancreatic function changes after acute pancreatitis. Pancreas 2011;40:1006–1011.

5. Owen OE, Caprio S, Reichard GA, et al. Ketosis of starvation: a revisit and new perspectives. Clin Endocrinol Metab 1983;12:359–379.

6. Patel A, Felstead D, Doraiswami M, et al. Acute starvation in pregnancy: a cause of severe metabolic acidosis. Int J Obstet Anesth 2011;20:253–256.

7. Wood ET, Kinlaw WB. Nondiabetic ketoacidosis caused by severe hyperthyroidism. Thyroid 2004;14:628–630.

8. Cartwright MM, Hajja W, Al-Khatib S, et al. Toxigenic and metabolic causes of ketosis' and ketoacidotic syndromes. Crit Care Clin 2012;28:601–631.

9. Nakamura K, Inokuchi R, Doi K, et al. Septic ketoacidosis. Intern Med 2014;53:1071–1073.

10. Duarte R, Simoes DM, Franchini ML, et al. Accuracy of serum beta-hydroxybutyrate measurements for the diagnosis of diabetic ketoacidosis in 116 dogs. J Vet Intern Med 2002;16:411–417.

11. Henderson DW, Schlesinger DP. Use of a point-of-care beta-hydroxybutyrate sensor for detection of ketonemia in dogs. Can Vet J 2013;51:1000–1002.

12. Hoenig M, Dorfman M, Koenig A. Use of a hand-held meter for the measurement of blood beta-hydroxybutyrate in dogs and cats. J Vet Em Crit Care 2008;18:86–87.

13. O'Neill S, Drobatz K, Satyaraj E, Hess R. Evaluation of cytokines and hormones in dogs before and after treatment of diabetic ketoacidosis and in uncomplicated diabetes mellitus. Vet Immunol Immunopathol 2012;148:276–283.

14. Minamoto Y, Otoni CC, Steelman SM, et al. Alteration of the fecal microbiota and serum metabolite profiles in dogs with idiopathic inflammatory bowel disease. Gut Microbes 2015;6:33–47.

15. Pan Y, Larson B, Araujo JA, et al. Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. Br J Nutr 2010;103:1746–1754.

16. Mitsuhashi Y, Nagaoka D, Ishioka K, et al. Postprandial lipid-related metabolites are altered in dogs fed dietary diacylglycerol and low glycemic index starch during weight loss. J Nutr 2010;140:1815–1823.

17. Abbott Diabetes Care Inc. Precision Xtra Blood ß-Ketone Test Strips: Blood Ketone Test Strip Instructions for use. Alameda, CA: Abbott; 2011.

18. Sears KW, Drobatz KJ, Hess RS. Use of lispro insulin for treatment of diabetic ketoacidosis in dogs. J Vet Emerg Crit Care (San Antonio) 2012;22:211–218.

19. Walsh ES, Drobatz KJ, Hess RS. Use of intravenous insulin aspart for treatment of naturally occurring diabetic ketoacidosis in dogs. J Vet Emerg Crit Care (San Antonio) 2016;26:101–107.

20. Bresciani F, Pietra M, Corradini S, et al. Accuracy of capillary blood 3-β-hydroxybutyrate determination for the detection and treatment of canine diabetic ketoacidosis. J Vet Sci 2014;15:309–316.

21. Steiner JM, Newman S, Xenoulis P, et al. Sensitivity of serum markers for pancreatitis in dogs with macroscopic evidence of pancreatitis. Vet Ther 2008;9:263–273.

22. Mansfield CS, Anderson GA, O'Hara AJ. Association between canine pancreatic-specific lipase and histologic exocrine pancreatic inflammation in dogs: assessing specificity. J Vet Diagn Invest 2012;24:312.

23. Huth SP, Relford R, Steiner JM, et al. Analytical validation of an ELISA for measurement of canine pancreas-specific lipase. Vet Clin Pathol 2010;39:346–353.

24. Haworth MD, Hosgood G, Swindells KL, et al. Diagnostic accuracy of the SNAP and Spec canine pancreatic lipase tests for pancreatitis in dogs presenting with clinical signs of acute abdominal disease. J Vet Emerg Crit Care 2014;24:135–143.

25. Mawby DI, Whittemore JC, Fecteau KA. Canine pancreatic-specific lipase concentrations in clinically healthy dogs and dogs with naturally occurring hyperadrenocorticism. J Vet Intern Med 2014;28:1244–1250.