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Retrospective evaluation of acid–base analysis in dogs and cats with diabetic ketosis (2017–2021): 96 cases

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Abstract

Objective: To describe the acid–base balance of diabetic animals with ketosis and to identify underlying mechanisms of acid–base changes using semiquantitative analysis.

Design: Retrospective study.

Setting: University teaching hospital.

Animals: Eighty-one client-owned dogs and 15 client-owned cats with diabetes and concurrent ketosis presented to a university teaching hospital.

Interventions: None.

Measurements and Main Results: The medical records database was searched from January 2017 through December 2021 for dogs and cats with diabetes mellitus and ketones present in urine or blood samples that also had venous blood gas and serum biochemical assays performed within 24 hours of each other. Traditional analysis identified normal acid–base status in 20% of dogs and 7% of cats. A simple metabolic acidosis with an elevated anion gap was observed in 17% of dogs and 20% of cats, and a metabolic alkalosis was present in 4% of dogs and 7% of cats. The semiquantitative approach identified metabolic acid–base disorders in all animals. One or more acidifying processes were evident in 100% of dogs and 100% of cats, 1 or more alkalotic processes in 93% of dogs and 100% of cats, concurrent alkalotic and acidotic processes in 85% of dogs and 100% of cats, and unmeasured anions in all cases.

Conclusions: Dogs and cats with diabetic ketosis can have variable and complex acid–base disorders that may be better recognized using semiquantitative analysis. Diagnostic criteria such as low pH or a high anion gap may prevent the clinical recognition of diabetic ketoacidosis.

KEYWORDS
diabetic ketoacidosis, lactate, metabolic acidosis, semiquantitative acid–base analysis, traditional acid–base analysis

Abbreviations: AG, anion gap; DKA, diabetic ketoacidosis.

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe, life-threatening complication of diabetes mellitus.[1] Commonly reported abnormalities in dogs and cats with DKA include acid–base and electrolyte derangements, dehydration, azotemia, and hyperlactatemia.[2]

In people, the biochemical criteria for the clinical diagnosis of DKA include hyperglycemia with a venous pH <7.3 and evidence of urine or serum ketones.[3] Although similar criteria have been applied in veterinary medicine, hyperglycemia, a pH <7.3 to 7.35, and evidence of ketones are considered core to the diagnosis; however, specific cutoff values for biochemical parameters have varied among studies.[1,4–6] When using such criteria, a high anion gap (AG) metabolic acidosis has been reported as the most common acid–base abnormality in dogs and cats with DKA.[4,5] Despite the widespread understanding that DKA causes acid–base derangements, to date, the actual acid–base disorders present in dogs and cats with DKA have been poorly described in the literature.

The origin of metabolic acidosis in patients with DKA is complex. Despite common beliefs, ketone bodies are not acids, and the protons associated with their production come from concurrent metabolic changes, such as adipose tissue lipolysis.[7] Animals with DKA may also present with concurrent hyperlactatemia or uremia, both of which are additional causes of metabolic acidosis.[6] Conversely, processes that cause metabolic alkalosis, such as hypochloremia due to gastric acid loss or contraction alkalosis from hypovolemia, may be present simultaneously in animals with DKA, as has been reported in people.[3,8–12] The presence of a concurrent alkalinizing process can result in the absence of acidemia (the absence of a low pH) in animals with DKA. The presence of a concurrent metabolic alkalinizing process can complicate the clinical recognition of DKA and may skew reporting of DKA in the literature, which has generally used diagnostic criteria including low pH.[6]

The semiquantitative approach to acid–base analysis identifies metabolic acidifying and alkalinizing processes.[13] The 5 processes evaluated using the semiquantitative approach are changes in plasma sodium, chloride and lactate concentrations, and serum phosphorous and albumin concentrations.[13] Given that animals with DKA can have numerous concurrent electrolyte and metabolic derangements, the semiquantitative approach to acid–base analysis may allow a better understanding of the pathophysiology of this disease than traditional acid–base analysis.

The primary objective of the current study was to describe the traditional and semiquantitative acid–base evaluations of diabetic dogs and cats with ketosis. We hypothesized that diabetic dogs and cats with ketosis would have complex metabolic processes with multiple coexisting acidotic and alkalotic effects.

2 | MATERIALS AND METHODS

The electronic medical records database of the University of California, Davis, William R. Pritchard Veterinary Medical Teaching Hospital was searched for dogs and cats with both point-of-care acid–base and electrolyte[a,b,c] and serum biochemistry panels[d,e] performed during a 5-year period occurring between January 2017 and December 2021, the results of which showed a blood glucose ≥11.1 mmol/L (200 mg/dL), the presence of ketones in either serum or urine, and a clinical diagnosis of diabetes mellitus. For the purpose of this study, the disease process present in this patient population will be called diabetic ketosis. Exclusion criteria were a blood glucose <11.1 mmol/L (<200 mg/dL)[a,b,c], absence of ketones, or if there was no acid–base and electrolyte panel in conjunction with a chemistry panel obtained and run within 24 hours of each other. If the same patient fulfilled these criteria more than once during the study period, only the first visit was included. Demographic data including species, breed, age, sex, reproductive status, and body weight were recorded. Additionally, the clinical diagnosis, discharge status, presenting service, and duration of hospitalization were recorded. Discharge status was reported as alive, euthanized, or natural death.

TABLE 1 Concurrent conditions of 81 dogs and 15 cats diagnosed with diabetic ketosis.

Disease process	Dogs, *N* (%)	Cats, *N* (%)
Gastrointestinal disease	37 (45%)	6 (40%)
Renal or urinary disease	6 (7%)	3 (20%)
Neoplasia	6 (7%)	0
Hepatobiliary	3 (4%)	2 (13%)
Infectious	3 (4%)	2 (13%)
Endocrine	4 (5%)	0
Respiratory	3 (4%)	0
Intracranial	2 (3%)	0
Cardiovascular	0	1 (7%)
Other	17 (21%)	1 (7%)

Coexisting disease processes were categorized based on the diagnosis listed by the primary clinician in the medical record, as shown in Table 1. For the purposes of the current study, the category of "gastrointestinal disease" included pancreatitis. If a disease process did not fit one of the classifications listed, it was included in the "other" category.

Traditional acid–base analysis and calculation of the AG were performed using the pH, bicarbonate concentration, P_vCO_2, and the sodium, chloride, and potassium concentrations measured or calculated by the blood gas machine. Semiquantitative acid–base analysis was performed using the plasma lactate and electrolyte (Na^+ and Cl^-) concentrations and standard base excess values from the blood gas machine, while the albumin and phosphorous concentrations were obtained from the serum biochemistry panel[d,e].

2.1 | Acid–base analysis

The blood gas analyzer calculated bicarbonate concentration and standard base excess using the Henderson–Hasselbalch and van Slyke

TABLE 2 Diagnostic criteria for traditional acid–base analysis.[13]

Dogs	Cats
1. Simple disturbances a. Metabolic acidosis: pH < 7.32, HCO_3^- < 18 mmol/L, $P_vCO_2 = 40 - (\Delta HCO_3^- \times 0.7) \pm 3$ b. Metabolic alkalosis: pH > 7.42, HCO_3^- > 26 mmol/L, $P_vCO_2 = 40 + (\Delta HCO_3^- \times 0.7) \pm 3$ c. Respiratory acidosis: pH < 7.32, P_vCO_2 > 45 mm Hg, $HCO_3^- = 22 + (0.15–0.35 \times \Delta P_vCO_2) \pm 2$ d. Respiratory alkalosis: pH > 7.43, P_vCO_2 < 37 mm Hg, $HCO_3^- = 22 - (0.25–0.55 \times \Delta P_vCO_{2)} \pm 2, \Delta P$ 2. Mixed disturbances Value in the secondary system not within predicted range 3. Metabolic acidosis further classified by anion gap: $AG = (Na^+ + K^+) - (HCO_3^- + Cl^-)$ High anion gap metabolic acidosis: AG > 23.5 mmol/L	1. Simple disturbances a. Metabolic acidosis: pH < 7.34, HCO_3^- < 18 mmol/L b. Metabolic alkalosis: pH > 7.43, HCO_3^- > 26 mmol/L c. Respiratory acidosis: pH < 7.34, P_vCO_2 > 39 mm Hg d. Respiratory alkalosis: pH > 7.43, P_vCO_2 < 34 mm Hg 2. Mixed disturbances Compensation was not calculated for cats; if abnormalities were present in both $PvCO_2$ and HCO_3^-, it was reported as 2 coexisting abnormalities (mixed disorder). 3. Metabolic acidosis further classified by anion gap Metabolic acidosis associated with increased AG: AG > 20 mmol/L Metabolic acidosis not associated with increased AG: AG ≤ 20 mmol/L

Abbreviation: AG, anion gap.

equations.[14,15] The analyzer used 0.03 mmol/L/mm Hg as the value for CO_2 solubility in plasma. Calculated acid–base variables were derived from measured acid–base, metabolite, and electrolyte values from previously established equations (Table 2).[13] Plasma electrolyte and lactate concentrations were measured in millimoles per liter, serum phosphate concentrations were measured in milligrams per deciliter, and serum albumin concentrations were measured in grams per deciliter. A traditional acid–base diagnosis was made for each dog and cat, as outlined in Table 2. The semiquantitative acid–base diagnosis is outlined in Table 3.[13] For venous canine blood, previously published reference intervals for pH, PCO_2, bicarbonate, AG, and electrolytes established by Vanova et al. were used.[16] For venous feline blood, reference intervals established according to the American Society for Veterinary Clinical guidelines, based on data from 40 healthy cats at the authors' institution using the point-of-care blood gas machine, were used.[17] The mid-normal values used in the semiquantitative formulas were determined as the central values of the appropriate reference intervals for the machine used.

2.2 | Statistical methods

Normality was assessed with a Shapiro–Wilk test[f]. Normally distributed data are presented as mean ± SD, and nonnormally distributed data are presented as median (range). Due to the low numbers of cats included, all data for this species are presented as median (range).

3 | RESULTS

A total of 152 dog and 53 cat patients were identified in the initial database search. Seventy-one dogs and 38 cats were excluded due to incomplete data or multiple visits; therefore, a total of 81 dogs and 15 cats were included in the study. The median age for dogs was 10 years (2–18 y), and the median body weight for dogs was 7.8 kg (2.4–56.2 kg). There were 41 neutered male dogs, 33 neutered female dogs, 3 intact male dogs, and 4 intact female dogs. The population of 81 dogs included 23 mixed breed dogs, 6 Chihuahuas, 6 Labrador Retrievers, 6 Toy Poodles, 4 Miniature Schnauzers, 3 Pomeranians, 3 Pugs, 3 Miniature Poodles, 3 Yorkshire Terriers, 2 Jack Russell Terriers, 2 Miniature Pinschers, 2 Norfolk Terriers, 2 West Highland White Terriers, and 1 each of multiple other breeds. The median age of cats was 10 years (0.5–15 y), and the median body weight was 4.6 kg (1.9–9.8 kg). Of the 15 cats, there were 12 neutered male cats, 2 neutered female cats, and 1 intact female cat. Breeds included 9 domestic shorthairs, 2 domestic medium hairs, 2 domestic longhairs, 1 Siamese, and 1 Bengal. Of the 81 dogs diagnosed with diabetic ketosis, 70 were presented through the emergency service, 3 through the internal medicine service, 7 through the ophthalmology service, and 1 through the neurology service. All of the 15 cats diagnosed with diabetic ketosis were presented through the emergency service.

Of the 81 dogs, 63 of 81 (78%) survived to discharge, 14 (17%) were euthanized, and 4 (5%) died. Of the 15 cats, 14 of 15 (93%) survived to discharge, and 1 (7%) was euthanized. The median duration of hospitalization in dogs was 4 days (1–14 d), and the median duration of hospitalization in cats was 5 days (1–11 d).

Forty-two of 81 (52%) dogs and 9 of 15 (60%) cats had been previously diagnosed with diabetes mellitus, with the remaining population of each group being newly diagnosed at the time of presentation with diabetic ketosis. Clinical diagnoses of concurrent diseases at the time of diabetic ketosis diagnosis for both dogs and cats are summarized in Table 1, with gastrointestinal diseases being the most commonly identified coexisting comorbidity.

Acid–base, electrolyte, glucose, and plasma lactate values for all dogs and cats are summarized in Tables 4 and 5. Four of the samples in dogs were arterial, with the remaining samples in dogs and all cat samples being venous. The median pH in dogs was 7.259 (6.913–7.459) and in cats was 7.236 (6.917–7.469), with 22 of 81 (27%) dogs and 3 of 15 (20%) cats having a pH >7.35. Traditional acid–base analysis revealed an abnormality in 65 of 81 (80%) dogs and 14 of 15 (93%) cats, with simple disorders present in 57 of 81 (70%) dogs and 4 of 15 (27%) cats. A metabolic acidosis with increased AG was the most common simple dis-

TABLE 3 Formulas for semiquantitative acid–base analysis.[13]

Parameter	Formula
Free water effect	
Dogs	0.25 × (measured [Na+] – mid-normal [Na+])
Cats	0.22 × (measured [Na+] – mid-normal [Na+])
Corrected chloride	Measured [Cl^-] × (mid-normal [Na^+]/ measured [Na^+])
Chloride effect	Mid-normal [Cl^-] – corrected [Cl^-]
Phosphate effect	0.58 × (mid-normal [phosphorous] – measured [phosphorous])
Albumin effect	3.7 × (mid-normal [albumin] – measured [albumin])
Lactate effect	−1 × measured [lactate]
Sum of effects	Sum = Free water effect + chloride effect + phosphate effect + albumin effect + lactate effect
Unmeasured anion (XA) effect	XA = Base excess – sum of effects

Semiquantitative acid–base analysisFree water effect
- Dilutional acidosis: Free water effect <−1.25 mmol/L
- Contraction alkalosis: Free water effect >1.0 mmol/L

Chloride effect:
- Acidosis: Chloride effect <−5.0 mmol/L
- Alkalosis: Chloride effect >5.0 mmol/L

Albumin effect:
- Acidosis: Albumin effect <−2.0 mmol/L
- Alkalosis: Albumin effect >2.0 mmol/L

Phosphorous effect:
- Acidosis: Phosphorous effect <−1.0 mmol/L
- Alkalosis: Phosphorous effect >1.0 mmol/L

Lactate effect:
- Acidosis: Lactate effect <−2.0 mmol/L

Unmeasured anions effect:
- Unmeasured acids: XA = 0.5 mmol/L
- Unmeasured alkalis: XA >0.5 mmol/L

Note: Mid-normal values were determined as the central value of the reference interval. Albumin, g/dL; phosphorous, mg/dL; electrolytes and lactate, mmol/L.

order in both dogs and cats (Table 6). A total of 47 of 81 (58%) dogs and 12 of 15 (80%) cats had a metabolic acidosis as either a simple disorder or part of a mixed disorder. A primary metabolic alkalosis was evident in 3 of 81 (4%) dogs and 1 of 15 (7%) cats. Mixed disorders were more common in cats (10/15 [67%]) than simple disorders. Traditional acid–base analysis indicated a normal acid–base balance in 16 of 81 (20%) dogs and 1 of 15 (7%) cats.

The semiquantitative approach identified metabolic acid–base disorders in all 81 dogs and 15 cats, with 100% of dogs and cats exhibiting at least 1 acidotic process (Table 7). The most common abnormalities were unmeasured anions in 100% of dogs and cats, an alkalotic chloride effect in 69 of 81 (85%) dogs and 14 of 15 (93%) cats, a dilutional acidosis in 66 of 81 (81%) dogs and 10 of 15 (67%) cats, and lactic acidosis in 45 of 81 (56%) dogs and 4 of 15 (27%) cats. One or more quantifiable alkalotic processes were present in 75 of 81 (93%) dogs and 15 of 15 (100%) cats. Concurrent alkalotic and acidotic processes were present in 69 of 81 (85%) dogs and 15 of 15 (100%) cats.

4 | DISCUSSION

The current study evaluates the acid–base balance in dogs and cats with diabetic ketosis using both the traditional and semiquantitative approaches. Metabolic acidosis as a sole disorder or as part of a mixed acid–base disorder was the most commonly identified acid–base abnormality using traditional analysis. Complex acid–base abnormalities were frequent in this population, whether the traditional or semiquantitative approach was applied, with respiratory acid–base changes and multiple, concurrent metabolic acid–base processes found to occur commonly. The signalment of the dogs and cats included in this study is similar to previous reports, with older-aged patients being more frequently affected than younger ones. The survival of animals in this study was also similar to previous reports, although the duration of hospitalization for the current study population was shorter than described in previous studies.[1,18,19] Differences in length of stay may have been due to differences in treatments and case management strategies among institutions. It is notable that previous studies were published 10–29 years ago and thus may not reflect the current standard of care. Similar to previous veterinary literature, in the current study, gastrointestinal conditions were the most commonly identified coexisting disease processes in both dogs and cats.[1,5,18,19] In traditional acid–base analysis, a high-AG metabolic acidosis is the classically described abnormality associated with DKA.[20] This was largely true in this study of animals with diabetes and ketosis, but only 17% of dogs had a simple disorder of a high-AG metabolic acidosis. Thirty-nine percent of dogs had a high AG metabolic acidosis when dogs

TABLE 4 Venous and arterial acid–base, electrolyte, and lactate values in 81 dogs with diabetic ketosis.

Parameter	Result
pH	7.253 (6.913–7.459)
PCO_2 (mm Hg)	34.2 (16.0–84.3)
Bicarbonate (mmol/L)	15.9 ± 6.7
Glucose (mg/dL) (mmol/L)	466 (240–1057) 25.9 (13.3–58.7)
Sodium (mmol/L)	140 ± 8.5
Potassium (mmol/L)	3.8 ± 0.8
Chloride (mmol/L)	106 (69–127)
Chloride corrected (mmol/L)	105.4 (71.8–126.1)
Albumin (g/dL) (g/L)	3.6 (1.7–4.8) 36 (17–48)
Lactate (mmol/L)	2.2 (0.5–8.4)
Base excess (mmol/L)	−10.1 ± 7.9
Anion gap (mmol/L)	23.7 ± 7.2
Free water effect (mmol/L)	−3.0 ± 2.1
Chloride effect (mmol/L)	10.1 (−10.6 to 43.7)
Albumin effect (mmol/L)	0.93 (−3.5 to 8.0)
Phosphate effect (mmol/L)	−0.41 (−7.3 to 1.3)
Lactate effect (mmol/L)	−2.2 (−8.4 to −0.5)
Sum of effects (mmol/L)	8.0 ± 7.5
Unmeasured anions (mmol/L)	−15.6 (−49.7 to −3.9)

Note: Data are presented as mean ± SD or median (range).

with simple and mixed disorders were considered together. Metabolic acidosis with normal AG was a common finding in dogs, and approximately 16% of dogs and 7% of cats had a normal acid–base balance with traditional analysis. Had the classic DKA diagnostic criteria of a pH <7.35 been used, only 63% of dogs and 56% of cats in this study would have been included. Animals with diabetic ketosis are expected to have a metabolic acidosis, although the ketone bodies acetoacetate, β-hydroxybutyrate, and acetone are not acids. The production of hydrogen ions is the result of concurrent metabolic derangements such as adipose tissue lipolysis, β-oxidation, and increased coenzyme A synthesis.[7] As a result, the presence of ketones coincides with an increased acid load in the body. Despite this, animals can present in diabetic ketosis with a normal or even a high pH, as demonstrated by the results of this study.

Metabolic alkalosis has been previously reported in patients with DKA in both the human[8–12] and veterinary[6] literature. In the current study, a metabolic alkalosis was evident in 5 (6%) dogs and 2 (13%) cats as either a primary disorder or part of a mixed acid–base abnormality. Because pH is used as part of the diagnostic criteria to identify patients with DKA in the veterinary literature, it is likely that many previous studies would not have included this subset of patients, despite the fact they had diabetic ketosis. The underlying causes of metabolic alkalosis in the dogs and cats with diabetic ketosis in this study are best explained using the semiquantitative approach to acid–base analysis.

Unlike traditional acid–base analysis where evaluation of metabolic acid–base balance relies on bicarbonate concentration, which reflects the cumulative impact of all major, coexisting metabolic acid–base processes, the semiquantitative approach allows for the identification of individual processes contributing to the overall metabolic acid–base status. All animals in this study had at least 1 metabolic acid–base abnormality identified with the semiquantitative approach. In contrast, 20% of dogs and 7% of cats were found to have a normal metabolic acid–base balance with the traditional analysis. An alkalotic effect associated with a decrease in corrected chloride concentration was the most commonly identified quantifiable alkalotic effect. This is most likely due to gastric loss of hydrochloric acid through vomiting, which is consistent with gastrointestinal problems being the most common concurrent disease processes in this population. Concurrent metabolic alkalosis with the metabolic acidosis associated with ketosis can lead to a final pH that is normal or elevated, as seen in several animals in this study, further emphasizing the limitation of using blood pH as part of the diagnostic criteria for DKA.

A common acidifying effect identified by semiquantitative analysis in this population of dogs and cats with diabetic ketosis was dilutional acidosis, evidenced by hyponatremia. Dilutional acidosis can be most simply explained by the expansion of the extracellular fluid space with nonbicarbonate-containing fluid, leading to dilution of the bicarbonate concentration and a subsequent acidosis. More complex explanations of this acid–base process are available elsewhere.[22,23] Hyponatremia is expected in the hyperglycemic patient secondary to hyperglycemia-induced free water shifts from the intracellular space to the extracellular space.[24] Hypoalbuminemia leading to an alkalotic albumin effect occurred in 30% of dogs in the current study, which is most likely the consequence of the concurrent disease processes. In comparison, hypoalbuminemia was uncommon in cats with diabetic ketosis in this study.

In acid–base evaluation, the presence of unmeasured anions indicates the presence of added acids in the system. A common method used for identification of unmeasured anions is the AG.[25] The expected concentrations of electrolytes and bicarbonate for the specific analyzer will dictate the expected reference interval for the AG.[25] An increased AG was present in approximately 40% of dogs and 67% of cats in this study. Because ketones were present in all animals in this study, it would be expected that they would all have an elevated AG, considering ketones are anions not measured in the acid–base/electrolyte or serum biochemistry panels. The reference interval for a normal AG is wide enough, however, that a patient could have some increase in unmeasured anions without exceeding the high end of the reference interval for AG. Additionally, when using traditional acid–base analysis, the sensitivity of the AG to detect the presence of unmeasured anions is reduced by concurrent hypoalbuminemia.[26] The high prevalence of hypoalbuminemia in dogs in this study suggests that many dogs with diabetic ketosis could be misidentified as non-ketotic if traditional acid–base analysis and AG were used as the primary screening tool for diabetic ketoacidosis. The use of AG alone to rule out the presence of unmeasured anions in suspected DKA is not recommended based on the results of the current study.

TABLE 5 Venous acid–base, electrolyte, and lactate values in 15 cats with diabetic ketosis.

Parameter	Median	Interquartile range	Range
pH	7.236	7.068–7.299	6.917–7.469
PCO_2 (mm Hg)	36.2	30.3–41.2	20.6–47
Bicarbonate (mmol/L)	13.2	9.7–17.9	6.7–32.7
Glucose (mg/dL) (mmol/L)	489 27.1	266–582.5 14.7–32.4	243–1451 13.5–80.6
Sodium (mmol/L)	144	141.5–150	131–169
Potassium (mmol/L)	3.4	3.05–3.75	2.3–5.3
Chloride (mmol/L)	96	93.5–105.5	74–127
Chloride corrected (mmol/L)	104.5	97.2–110.1	85.3–116.1
Albumin (g/dL) (g/L)	3.6 36	3.3– 39 33– 39	2.7–4.1 27–41
Lactate (mmol/L)	1.7	1.55– 2.1	1.0 –5.7
Base excess (mmol/L)	−14.5	−17.05 to −7.35	−23 to 8.6
Anion gap (mmol/L)	28.9	21.1– 33.5	18.4 –43
Free water effect (mmol/L)	−2.31	−2.86 to −0.99	−5.2 to 3.2
Chloride effect (mmol/L)	18.6	12.9– 25.8	6.9–37.7
Albumin effect (mmol/L)	−0.7	−1.7 to 0.6	−2.6 to 2.6
Phosphorous effect (mmol/L)	0.7	−0.1 to 1.3	−5.3 to 2.2
Lactate effect (mmol/L)	−1.7	−2.1 to −1.6	−5.7 to −1.0
Sum of effects (mmol/L)	16.6	9.2–20.8	2.8–32.6
Unmeasured anions (mmol/L)	−29.5	−31.8 to −23.0	−47.3 to −9.0

TABLE 6 Traditional acid–base diagnosis of 81 dogs and 15 cats with diabetic ketosis.

Acid–base diagnosis	Dogs, *N* (%)	Cats, *N* (%)
Normal acid–base balance	16 (20%)	1 (6.7%)
Simple disorders	57 (70%)	4 (27%)
Respiratory acidosis	10 (12.3%)	0 (0%)
Respiratory alkalosis	1 (1%)	0 (0%)
Metabolic acidosis with normal AG	14 (17%)	0 (0%)
Metabolic acidosis with elevated AG	29 (36%)	3 (20%)
Metabolic alkalosis	3 (4%)	1 (7%)
Mixed disorders	8 (10%)	10 (67%)
Respiratory acidosis with metabolic acidosis and normal AG	2 (3%)	0 (0%)
Respiratory acidosis with metabolic acidosis and elevated AG	1 (1%)	4 (27%)
Respiratory alkalosis with metabolic acidosis and normal AG	1 (1%)	2 (13.3%)
Respiratory alkalosis with metabolic acidosis and elevated AG	2 (3%)	3 (20%)
Respiratory acidosis with metabolic alkalosis	2 (3%)	0 (0%)
Respiratory alkalosis with metabolic alkalosis	0 (0%)	1 (7%)

Abbreviation: AG, anion gap.

TABLE 7 Semiquantitative approach acid–base diagnosis of 81 dogs and 15 cats with diabetic ketosis based on venous or arterial blood gas and biochemical evaluation.

Metabolic acid–base diagnosis	Dogs, *N* (%)	Cats, *N* (%)
One or more acidotic processes	81 (100%)	15 (100%)
One or more alkalotic processes	75 (93%)	15 (100%)
Both alkalotic and acidotic processes	69 (85%)	15 (100%)
Dilutional acidosis	66 (82%)	10 (67%)
Acidotic chloride effect	1 (1%)	0 (0%)
Alkalotic chloride effect	69 (85%)	14 (93%)
Acidotic albumin effect	6 (7%)	3 (20%)
Alkalotic albumin effect	25 (32%)	1 (7%)
Acidotic phosphate effect	25 (27%)	2 (13%)
Lactic acidosis	45 (56%)	4 (27%)
Unmeasured anions	81 (100%)	15 (100%)
Unmeasured cations	0 (0%)	0 (0%)

All animals in this study had unmeasured anions identified using the semiquantitative approach to acid–base analysis, suggesting that this method has a greater sensitivity to detect unmeasured anions than AG, a finding consistent with previously reported data.[25] The calculated unmeasured anion effect is not influenced by the presence of

hypoalbuminemia, which should improve its performance in a critically ill patient population compared with the AG. However, it is important to note that the calculation of unmeasured anions by the semiquantitative method has not been rigorously evaluated for its accuracy to detect a known quantity of unmeasured anions across a variety of conditions.

The presence of ketosis in a sick diabetic patient with a normal or increased pH raises the question of terminology. There have been suggestions to use "diabetic ketosis" or "diabetic ketoalkalosis" instead of DKA in these situations.[8,27] The aberrant metabolism associated with the production of ketones is associated with increased acid production and, as such, it seems reasonable to call this disease process DKA, regardless of the concurrent pH.[28,29] More importantly in the clinical setting, however, is to recognize that patients with DKA can have complex disease states and variable acid–base balance in order to avoid misdiagnosis.

This study has several limitations. First, we allowed up to 24 hours between point-of-care acid–base, electrolyte, and plasma lactate measurements and collection of the serum biochemistry sample. We cannot rule out the possibility that therapies given between the 2 sample collections may have influenced the results or led to discordant findings. However, it is standard practice at the authors' institution to draw heparinized, serum, and EDTA whole blood samples simultaneously at the time of initial IV catheter placement, so it is likely that most analyzed values resulted from a single blood draw from each patient. Another limitation is the small number of cats included in this study; a larger study population should be evaluated to confirm these findings in this species.

In conclusion, this study demonstrates that dogs and cats with the acid-producing condition of diabetic ketosis can have variable acid–base abnormalities and that mixed acid–base disorders are commonly identified. The use of a low pH or a high AG as part of the diagnostic criteria for DKA may prevent the clinical recognition of this disease process. The semiquantitative approach demonstrated that dogs and cats with DKA commonly have multiple coexisting acid–base abnormalities, and this approach may help clinicians tailor the diagnostic and therapeutic plan for an individual patient.

AUTHOR CONTRIBUTIONS

Lindsay N. Cuddy: Data curation; formal analysis; writing—original draft; writing—review and editing. **Kate Hopper**: Conceptualization; formal analysis; writing—review and editing. **Jamie M. Burkitt-Creedon**: Writing—review and editing. **Steven E. Epstein**: Conceptualization; formal analysis; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

Dr. Burkitt-Creedon and Dr. Epstein are editors of the Journal but only participated in the peer review process as authors. The authors declare no other conflicts of interest.

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ENDNOTES

[a] ABL 705, Radiometer Medical A/S, Copenhagen, Denmark.
[b] ABL 800, Radiometer Medical A/S.
[c] ABL 815, Radiometer Medical A/S.
[d] Chemistry analyzer, Hitachi 917, Roche Diagnostics, Indianapolis, IN.
[e] Chemistry analyzer, Hitachi c501, Roche Diagnostics.
[f] GraphPad Prism 9.0 La Jolla, CA

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