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Acid-base abnormalities in dogs with diabetic ketoacidosis: a prospective study of 60 cases

Distúrbios ácido-base em cães com cetoacidose diabética: estudo prospectivo de 60 casos

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Abstract

Diabetic ketoacidosis (DKA) is considered a typical high anion gap metabolic acidosis due to the retention of ketoanions. The objective of this study was to describe the acid-base disturbances of dogs with DKA and further characterize them, according to their frequency, adequacy of the secondary physiologic response, and occurrence of mixed disturbances. Sixty dogs with DKA were enrolled in the study. Arterial blood pH and gas tensions, plasma electrolytes, serum β-hydroxybutyrate (β-OHB), glucose, albumin and urea concentrations were determined for all dogs included in the study. All dogs were evaluated individually and systematically by the traditional approach to the diagnosis of acid-base disorders. Most of the dogs had a high anion gap acidosis, with appropriated respiratory response (n = 18; 30%) or concurrent respiratory alkalosis (n = 14; 23%). Hyperchloremic acidosis with moderated to marked increases in β-OHB was observed in 18 dogs (30%) and 7 of these patients had concurrent respiratory alkalosis. Hyperchloremic acidosis with mild increase in β-OHB was observed in 6 dogs (10%). Four dogs (7%) had a high anion gap acidosis with mild increase in β-OHB and respiratory alkalosis. Most of dogs with DKA had a high anion gap acidosis, but mixed acid-base disorders were common, chiefly high anion gap acidosis and concurrent respiratory alkalosis, and hyperchloremic acidosis with moderated to marked increases in serum β-OHB.

Keywords: Endocrinology. Diabetes mellitus. Acid-base balance. Anion gap.

Resumo

A cetoacidose diabética (CAD) é considerada um quadro típico de acidose metabólica e aumento do *anion gap*, devido à retenção de cetoânions. O objetivo deste estudo foi descrever os distúrbios ácido-base de cães com CAD e ainda caracterizá-los, de acordo com sua frequência, adequação da resposta secundária fisiológica e ocorrência de distúrbios mistos. Sessenta cães com CAD foram incluídos no estudo. O pH e hemogasometria arteriais, eletrólitos plasmáticos, glicose, β-hidroxibutirato (β-OHB), albumina e ureia séricos foram determinados para todos os cães incluídos no estudo. Todos os cães foram avaliados individualmente e de forma sistemática pela abordagem tradicional para o diagnóstico de distúrbios ácido-básicos. A maioria dos cães tinha uma acidose metabólica com aumento do *anion gap*, com resposta respiratória apropriada (n = 18; 30%) ou alcalose respiratória concomitante (n = 14; 23%). A acidose hiperclorêmica com aumento moderado a marcante do β-OHB sérico foi observada em 18 cães (30%) e sete desses pacientes tinham alcalose respiratória concomitante. A acidose hiperclorêmica com aumento discreto do β-OHB sérico foi observada em seis cães (10%). Quatro cães (7%) tinham acidose metabólica com aumento discreto do β-OHB e alcalose respiratória. A maioria dos cães com CAD tinha uma acidose metabólica com aumento do *anion gap*, mas distúrbios ácido-básicos mistos foram comuns, principalmente, acidose metabólica com aumento do *anion gap* e alcalose respiratória concomitante e acidose hiperclorêmica associada a um aumento de moderado a marcante do β-OHB sérico.

Palavras-chave: Endocrinologia. Diabetes mellitus. Equilíbrio ácido-base. *Anion gap*.

Introduction

Diabetic ketoacidosis (DKA) is a common complication of diabetes mellitus in dogs, characterized by extreme metabolic alterations, including hyperglycemia, metabolic acidosis dehydration and loss of electrolytes[1]. The basic underlying mechanism of DKA is a relative or absolute reduction of circulating

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insulin coupled with a concomitant elevation of glucagon and other counter regulatory hormones such as cortisol and catecholamines. These hormonal alterations lead to increased hepatic gluconeogenesis and impaired glucose utilization in peripheral tissues, which results in hyperglycemia. The combination of insulin deficiency and increased counter-regulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue and to uncontrolled hepatic fatty acid oxidation to ketoacids (β-hydroxybutyric and acetoacetic).

Ketoacids are released into the extracellular fluid and fully dissociate. The hydrogen ions formed are titrated by bicarbonate and other body buffers, resulting in metabolic acidosis. Primary hypobicarbonatemia causes acidemia that stimulates central and peripheral chemoreceptors, causing increases in tidal volume and, usually, respiratory rate. The secondary respiratory response to metabolic acidosis has been quantified in dogs and is predictable in magnitude[2].

The retention of ketoanions causes an increase in anion gap. This latter term refers to those plasma anions, other than chloride and bicarbonate, that balance the positive charges of plasma cations (sodium, potassium and other –unmeasured– cations)[3]. DKA is regarded as a typical high anion gap acidosis, but studies in human beings with DKA showed that the acid-base abnormalities of individual patients may be variable[4].

Albeit carrying a high mortality (approximately 30% in two case series[1,5], a few studies depict clinicopathologic data about dogs with DKA[5,6]. Often, many assumptions about DKA in dogs are generalized from data obtained from human beings and experimental studies in dogs. Since proper correction of the alterations in acid-base composition is an important part of the adequate management of DKA, the knowledge of these derangements is essential. The objective of this study was to describe the acid-base disturbances of dogs with naturally occurring DKA and further characterize them, according to their frequency, adequacy of the secondary physiologic response, and occurrence of mixed disturbances.

Material and Method

Between August, 2003, and August, 2006, we conducted a prospective, observational study of all dogs with DKA admitted to the intensive care unit of the Veterinary Teaching Hospital of the University of São Paulo, Brazil. Dogs were eligible for this study, if they had hyperglycemia (> 250 mg/dL), glucosuria, ketonuria, and plasma bicarbonate concentration below 18 mmol/L. For dogs with more than one admission to the hospital, data were collected only from the first episode in order to avoid that individual-specific characteristics could potentially bias results.

Thirty six clinically healthy dogs were selected for the reference range study. Dogs were of assorted breeds and body weight, with ages ranging from 1 to 15 y-old and were recruited from members of the hospital staff and school students. Dogs were considered healthy based on clinical examination and routine laboratory exams. All healthy dogs had serum glucose values within reference range (65 to 125 mg/dL) and negative urine glucose and ketones. Informed consent was obtained from the owners of all dogs included in the study. The experimental design was approved by two independent ethics committees of our institution.

Urine and blood samples from diabetic dogs were obtained before treatment with short-acting insulin or intravenous fluids. Arterial blood samples were collected from the femoral artery, using syringes containing lyophilized lithium heparin (BD Preset, Becton, Dickinson and Co., Plymouth, USA) and handled under anaerobic conditions until analysis, within 15 minutes after collection. For biochemical determinations, venous blood samples were collected, sera were harvest and stored at −70°C, until analyzed. Blood

and urine samples from healthy dogs were obtained before 10 AM, following an overnight fasting.

Serum β-hydroxybutyrate (β-OHB), glucose, albumin, lactate, and urea concentrations; plasma sodium, chloride and potassium concentrations; arterial blood gas tensions and pH, and presence of glucose or ketones in urine were determined for all dogs included in the study. Arterial blood pH, partial pressure of CO_2 ($PaCO_2$) and O_2 (PaO_2) determinations were performed with blood gas analyzer (OMNI 4, AVL Medical Instruments, Graz, Austria). Values of pH and blood gas determinations were automatically adjusted to rectal temperature. Plasma bicarbonate concentrations ($[HCO_3^-]$) were calculated by the Henderson-Hasselbalch equation. Electrolytes were determined by ion-specific methods using the OMNI 4 analyzer. Concentrations of β-OHB in serum were measured with the use of a liquid reagent (Autokit 3-HB, Wako Chemicals USA, Inc. Richmond, USA). For simplicity, we categorized the degree of ketonemia in "mild" (β-OHB ≤ 1.9 mmol/L), "moderate" (2.0 to 3.7 mmol/L) or "marked" (β-OHB ≥ 3.8 mmol/L). Other serum chemistry tests were performed by standard methods, with an automatic analyzer (Liasys, AMS, Rome, Italy). Urine ketones and glucose were assessed by urine dipstick tests (Combur, Roche Diagnostics, Mannheim, Germany).

All dogs included in the study were evaluated individually and systematically by the Van Slyke approach to the diagnosis of acid-base disorders[7]. Assuming all dogs had primary metabolic acidosis, the expected respiratory response was a 0.7 mm Hg decrease in $PaCO_2$ for each 1-mmol fall in plasma $[HCO_3^-]$[8].A deviation by more than 5.0 mm Hg from the predicted value of $PaCO_2$ indicated that a mixed acid-base disorder was present[2]. To calculate the expected secondary responses, the mean values of $PaCO_2$ and $[HCO_3^-]$ of the dogs from the reference range study (34.7 mm Hg and 21.3 mmol/L, respectively) were used as baseline levels for each variable. The plasma anion gap was calculated subtracting the sum of plasma chloride and $[HCO_3^-]$ concentrations from the sum of plasma sodium and potassium concentrations. An anion gap above the upper limit of the reference range (24 mEq/L) indicates the presence of high anion gap (or "normochloremic") acidosis. By convention, metabolic acidosis associated with an anion gap within reference range is termed "hyperchloremic acidosis". This approach has been described in details elsewhere[8].

Data were summarized as mean ± SD and range. Comparisons between specific subsets of the study group were performed *a posteriori*, using the Fisher's exact test for categorical variables, and the *t* test for comparisons involving continuous variables. Data were analyzed with computer software (SPSS for Windows 13.0, SPSS Inc., Chicago, USA). For all statistical analysis, a P value ≤ 0.05 was considered significant.

Results

Sixty dogs were enrolled in this study. The age of diabetic dogs ranged from 4- to 18-years (mean: 10 years). A predominance of females was observed: of the 60 dogs enrolled, 47 were females, and only 12 were spayed. Thirteen dogs were intact males. The study group was composed of 36 newly diagnosed diabetic dogs and 24 insulin-treated dogs. There was no statistical difference between insulin-treated and newly diagnosed diabetic dogs in any study variables, with the exception of serum β-OHB, whose mean was higher in untreated dogs (5.8 mmol/L vs. 4.3 mmol/L; $P = 0.027$). Laboratory data of the dogs included in study group are presented in table 1.

Comorbid conditions were suspected in 39 dogs, and included presumed hyperadrenocorticism (n = 13, five cases were subsequently confirmed); neoplasia (10; mammary neoplasia comprised 6 cases); pancreatitis (8); renal disease (4); urinary tract infection (3); subcutaneous abscess (1); and pyometra (1). Some dogs had more than one condition.

Table 1 - Laboratory values of the diabetic dogs on admission

Variable	Study group (n = 60)	Control group (n = 36)
	Mean ± SD (range)	Mean (reference values)
Arterial blood pH	7.296 ± 0.11 (7.001–7.491)	7.410 (7.37–7.46)
$PaCO_2$ (mm Hg)	23.6 ± 5.5 (13.9–34,5)	34.7 (29.0–41.0)
PaO_2 (mm Hg)	98.4 ± 17.0 (72.1–151.4)	94.0 (80–110)
$[HCO_3^-]$ (mmol/L)	11.6 ± 4.2 (5.1–17.6)	21.3 (18.0–25.0)
Na^+ (mmol/L)	139.0 ± 8.5 (121.7–165.2)	145.0 (139–152)
K^+ (mmol/L)	3.8 ± 0.9 (2.3–5.8)	4.0 (3.3–4.8)
Cl^- (mmol/L)	104.1 ± 10,0 (71.3–126.4)	110.0 (106–115)
Albumin (mg/dL)	2.8 ± 0.5 (2.0–4.0)	3.0 (2.0–3.5)
Anion gap (mEq/L)	27 ± 8.4 (11–52)	18 (11–24)
Glucose (mg/dL)	581 ± 284 (273–1,670)	95.0 (69–122)
Lactate (mmol/L)	4.8 ± 2.2 (1.7–12.9)	2.4 (0–5)
b-OHB (mmol/L)	5.2 ± 2.7 (0.06–11.2)	0.06 (0–0.11)
Urea (mg/dL)	80 ± 78 (16–378)	35 (15–47)

$PaCO_2$: partial pressure of CO_2; PaO_2: partial pressure of O_2; $[HCO_3^-]$: plasma bicarbonate; Na^+: plasma sodium; K^+: plasma potassium; Cl^-: plasma chloride; b-OHB: serum b-hydroxybutyrate

Acidemia was observed in 44 (approximately 73%) of the 60 dogs, and 14 (23%) dogs had arterial blood pH within reference range. Two dogs had mild alkalemia (7.491 and 7.487), acidosis (15.6 mmol/L and 17.3 mmol/L), and hypocapnia (21.4 mm Hg and 23.8 mm Hg, respectively). These cases could be interpreted as simple primary respiratory alkalosis, but both dogs had increases in β-OHB (6.9 mmol/L and 3.5 mmol/L), and signs of malaise, like vomiting and anorexia, suggesting a mixed disorder. Thus, they were not excluded from the study group.

Thirty five dogs had appropriated ventilatory response, and 25 dogs had concurrent respiratory alkalosis (Figure 1). These dogs had a mean decrement in $PaCO_2$ of 7.8 mm Hg below the expected respiratory response for their hypobicarbonatemia. Dogs with concurrent respiratory alkalosis had lower $[HCO_3^-]$ (mean: 9.7 mmol/L vs. 13.0 mmol/L; $P = 0.002$), lower plasma potassium concentrations (mean: 3.3 mmol/L vs. 4.2 mmol/L; $P < 0.001$), and a higher anion gap (mean: 30 mmol/L vs. 25 mmol/L; $P = 0.02$) than those with appropriated respiratory response. The mean β-OHB concentrations were identical between these subsets (5.2 mmol/L; $P = 0.94$). No difference was observed regarding to other variables. Also, the occurrence of concurrent illness in dogs with inappropriate ventilatory response was not different from those with appropriated response ($P = 0.59$). Acidemia was observed in 16 of the 25 dogs with concurrent respiratory alkalosis and in 28 dogs with appropriated response.

A high anion gap was observed in 36 patients (mean: 32.4 mEq/L) and the remaining 24 dogs

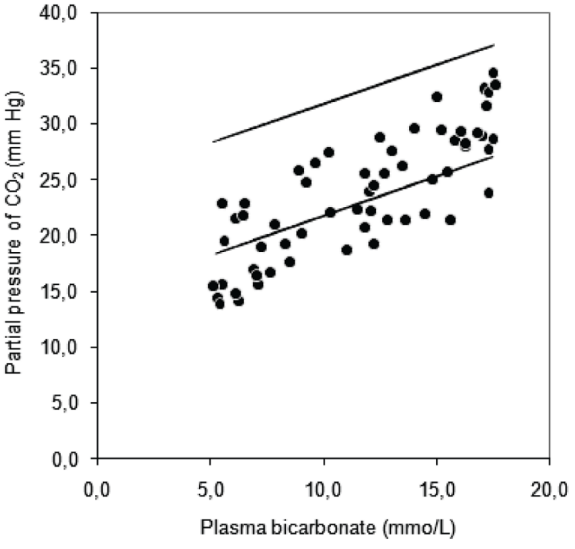

Figure 1 - Relationship between plasma partial pressure of CO_2 and plasma bicarbonate of 60 dogs with diabetic ketoacidosis. Parallel lines represent the limits of the expected secondary respiratory response

had hyperchloremic acidosis (mean: 19.1 mEq/L). These subsets had several differences which are depicted in table 2.

Dogs with high anion gap acidosis had moderated (n = 3) to marked (29) ketonemia. Four dogs with high anion gap had mild increase in their β-OHB concentrations, three of them were insulin-treated dogs and one had renal failure. Dogs with hyperchloremic acidosis had moderated (n = 7) to marked (11) ketonemia. Six dogs had a serum β-OHB concentration ≤ 1.9 mmol/L and 5 of them were insulin-treated dogs. There was no difference related to the occurrence of concurrent illness between dogs with high anion gap acidosis and dogs with hyperchloremic acidosis ($P = 0.10$). A summary of the acid-base disturbances observed in this series are presented in table 3.

Discussion and Conclusions

Dogs with DKA exhibited predominantly high anion gap acidosis, although multiple acid-base disturbances were observed, most notably mixed metabolic acidosis and respiratory alkalosis, and hyperchloremic acidosis with moderated to marked increases in serum β-OHB.

The reason for the inappropriate respiratory response is not clear. Concurrent metabolic acidosis and respiratory alkalosis may result from stimulation of the peripheral chemoreceptors by hypoxia or

Table 2 - Comparison of laboratory variables of dogs with anion gap acidosis and dogs with hyperchloremic acidosis

Variable	High anion gap acidosis (n = 36)	Hyperchloremic acidosis (n = 24)	*P* value
Arterial blood pH	7.269 ± 0.11 (7.001–7.491)	7.336 ± 0.09 (7.078–7.487)	0.015
$PaCO_2$ (mm Hg)	21.6 ± 4.7 (13.9–29.5)	26.5 ± 5.3 (14.2–34.5)	<0.001
PaO_2 (mm Hg)	98.4 ± 12.6 (72.1–151.4)	100.0 ± 21.9 (74.1–147.0)	0.55
$[HCO_3^-]$ (mmol/L)	10.0 ± 3.6 (5.1–16.1)	14.0 ± 3.9 (6.1–17.6)	<0.001
Na^+ (mmol/L)	140.1 ± 9.4 (121.7 – 165.2)	137.2 ± 6.7 (128.8–155.3)	0.20
K^+ (mmol/L)	3.6 ± 0.7 (2.3–5.7)	4.2 ± 1.0 (2.3–5.8)	0.02
Cl^- (mmol/L)	101.4 ± 10.6 (71.3–124.4)	108.2 ± 7.6 (96.9–126.4)	0.008
Albumin (mg/dL)	3.0 ± 0.5 (2.2–4.0)	2.6 ± 0.5 (2.0–4.0)	0.004
Glucose (mg/dL)	619 ± 328 (315–1.670)	523 ± 194 (273–990)	0.32
Lactate (mmol/L)	4.4 ± 2.0 (1.7–11,0)	4.9 ± 2.5 (1.7–12.9)	0.55
b-OHB (mmol/L)	6.2 ± 2.7 (0.6–11.2)	3.7 ± 1.8 (0.06–7.2)	<0.001
Urea (mg/dL)	100 ± 88 (22–378)	51 ± (16–199)	0.005

Data are mean ± SD and (range) except for urea. $PaCO_2$: partial pressure of CO_2; PaO_2: partial pressure of O_2; HCO_3^-: plasma bicarbonate; Na^+: plasma sodium; K^+: plasma potassium; Cl-: plasma chloride; b-OHB: serum b-hydroxybutyrate

Table 3 - Summary of the acid-base disturbances in 60 dogs with diabetic ketoacidosis

Type of acid-base disturbance	n (%)
High anion gap acidosis with moderated to marked ketonemia	18 (30%)
High anion gap acidosis with moderated to marked ketonemia and respiratory alkalosis	14 (23%)
Hyperchloremic acidosis with moderated to marked ketonemia	11 (18%)
Hyperchloremic acidosis with moderated to marked ketonemia and respiratory alkalosis	07 (12%)
Pure hyperchloremic acidosis	06 (10%)
High anion gap acidosis with mild ketonemia and respiratory alkalosis	04 (07%)

hypotension; stimulation of the afferent pulmonary reflexes, which occurs in intrinsic pulmonary diseases; or central stimulation, caused by Gram-negative sepsis, for example[9]. This mixed acid-base disorder have been reported in dogs with pyometra, salicylate toxicity,and severe babesiosis[10,11,12]. Except for pyometra, none of these conditions were documented in this series. Because hypocapnia is the expected physiologic response to metabolic acidosis, this mixed acid-base disorder may be difficult to recognize clinically, and the diagnosis can be made only by assessment of blood gases.

Metabolic acidosis and respiratory alkalosis are counterbalancing disorders, and a neutralizing effect on pH would be expected. But, in fact, 16 of the 25 dogs with concurrent respiratory alkalosis had acidemia. It has been demonstrated that dogs with induced metabolic acidosis and sustained chronic hypocapnia have worsening acidemia and acidosis, as a result of a maladaptive renal response to hypocapnia[13,14,15]. The chronic reduction in $PaCO_2$ causes bicarbonaturia and depresses the net acid excretion. The additional reduction in $[HCO_3^-]$, caused by the superimposed respiratory alkalosis, can possibly slower the recovery from metabolic acidosis. This paradoxical effect occurs because the renal adaption to hypocapnia is not mediated by extra- or intracellular $[H^+]$ but rather by the PCO_2, irrespective of the cause of its reduction[13,14,15].

It is noteworthy that dogs with concurrent respiratory alkalosis had hypokalemia. Dogs with exercise-induced acute respiratory alkalosis develop hypokalemia, possibly caused by translocation of potassium into cells as due to alkalemia[16]. Acute respiratory alkalosis causes hyperkalemia in non-anesthetized humans, possibly induced by a hypocarbonatemia-mediated increment in α-adrenergic activity[17]. In awake humans with chronic hypocapnia, plasma potassium falls, regardless the plasma $[HCO_3^-]$, but chronic respiratory alkalosis does not affect plasma potassium concentrations in conscious dogs[18,19].

Patients with DKA have total-body potassium depletion due to massive urinary potassium loss, secondary to osmotic diuresis, and further aggravated by vomiting and poor oral intake. However, plasma potassium concentrations can be normal or even elevated at the time of presentation because of hypoinsulinemia and diminished kaliuresis, due to renal dysfunction. These patients, with low or normal plasma potassium concentration, have severe total-body potassium depletion.

There is no evidence that dogs with concurrent respiratory alkalosis were sicker than those with appropriate ventilatory response: there was no difference between these subsets regarding to degree of acidemia, ketonemia and azotemia or the presence of concurrent illness. It may be argued that dogs with concurrent respiratory alkalosis have hypokalemia as a bystander feature of a more prolonged disease course, time enough for changes in renal acidification affects plasma $[HCO_3^-]$.

Our findings are similar to those observed in studies of human beings: a high proportion of patients with DKA is presented with hyperchloremic acidosis. However, most of our patients with an anion gap within the reference range (18 of 24 dogs), had moderate to marked hyperketonemia, suggesting that these cases do not had pure hyperchloremic acidosis, but rather, a mixed disorder of hyperketonemia and relative retention of chloride. In another series of dogs with DKA, Hume and co-workers found a lower proportion (23%) of dogs with an anion gap within the reference range[6]. This may be attributed to differences in criteria to define DKA. We made our definition of DKA intentionally broader to avoid exclusion of patients with mixed acid-base disorders. Therefore, our findings may not apply to other populations. Serum lactate concentration was significantly higher in dogs with DKA than in the healthy dogs in the present study, probably because of dehydration, but there was no difference between

dogs with high anion gap and dogs with hyperchloremic acidosis, suggesting that metabolic acidosis was caused by high serum ketone concentration.

The sensitivity of the anion gap to detect marked ketonemia is only fair (72%) and adjusting the anion gap values for albumin using a proposed equation did not improve sensitivity, probably because hypoalbuminemia was not a prominent feature in dogs with DKA.[20,21] Also, many factors can influence the anion gap. For example, dogs with experimentally induced hyperchloremic acidosis have a reduction in their value of anion gap[22]. This was credited to titration-related decrease in the net negative charge of plasma nonbicarbonate buffers, mainly the plasma proteins. So, changes in anion gap might be masked by offsetting changes in other electrolytes. Also, the reference range for anion gap in dogs is wide (11 to 24 mEq/L), probably due to biological and cumulative analytical variance.

Thus, one can conclude that these findings just reflect the inability of the anion gap to predict hyperketonemia. However, we interpret our data to indicate that anion gap may discriminate clinically relevant subtypes of DKA. Dogs with hyperchloremic acidosis, independently of having abnormal ketonemia, had milder acidosis and appear to have better preserved renal function, based on serum urea. Studies of human beings with DKA have showed that, patients able to maintain water and salt intake and thus with better preserved renal function, present on admission with variable degrees of hyperchloremic acidosis[4]. This is believed to the preferential urinary excretion of ketones as sodium and potassium salts and the relative retention of chloride, which has to be distributed in a smaller volume, due to dehydration[23]. Human patients presenting with hyperchloremic acidosis have a slower recovery from metabolic acidosis when compared to those with a high anion gap acidosis[4]. It was not possible to make any statement with regard to type of acidosis and its relation to the outcome of diabetic dogs, because the treatment had no systematic follow-up.

Another limitation of our study is that dogs with DKA were not submitted to broader evaluation to identify concurrent conditions that could cause mixed acid-base disorders. It should be noted, however, that dogs with DKA frequently present conditions such as vomiting and dehydration that *per se* can cause mixed acid-base disturbances. Furthermore, the exclusion of mixed acid-base disturbances cannot be made based solely on laboratory and other complimentary exams. Data must be interpreted in correlation with the knowledge of the underlying clinical picture.

In this study, a wide spectrum of acid-base disturbances could be appreciated, ranging from pure high anion gap acidosis to pure hyperchloremic acidosis. Concurrent respiratory alkalosis and, probably, variable degrees of relative hyperchloremia were common. Both conditions cause additional hypobicarbonatemia and, theoretically, can slower the recovery from metabolic acidosis. The impact of these abnormalities in the mortality or length of hospital stay of dogs with DKA merits further investigation.

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