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Diagnostic utility of different models used to assess the acid–base balance in cats with chronic kidney disease

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ABSTRACT

Metabolic acidosis is diagnosed based on the concentration of bicarbonate ions and partial pressure of carbon dioxide in arterial blood, although acid–base balance (ABB) disorders may also be diagnosed based on the serum ion concentrations in order to determine the values of strong ion difference (SID), anion gap (AG), corrected anion gap (AG_{corr}) and chloride/sodium ratio (Cl^-/Na^+). The aim of this study was to assess and compare the classic model, the value of the AG, AG_{corr}, and Cl^-/Na^+ in the diagnosis of ABB disorders in cats with chronic kidney disease (CKD). The study group consisted of 80 cats with CKD, divided into four groups based on the guidelines of the International Renal Interest Society (IRIS). The control group (C) included 20 healthy cats. Metabolic acidosis – diagnosed based on the classic model (Hendersson–Hasselbalch equation) – was found in IRIS group IV. AG, AG_{corr}, SID calculated for IRIS groups II, III and IV were lower than in group C, while the value of AG_{diff} and Cl^-/Na^+ in those groups was higher than in group C. We can conclude that ABB analysis using the classic model enabled the detection of ABB disorders in cats in stage IV CKD. However, the analysis of the AG, AG_{corr} and Cl^-/Na^+ values enabled the diagnosis of acid–base balance disorders in cats with IRIS stage II, III and IV CKD.

KEYWORDS

acid–base balance, anion gap, cats, CKD, metabolic acidosis

INTRODUCTION

Chronic kidney disease (CKD) commonly affects domestic cats (Brown et al., 2016). A study carried out in the United Kingdom has found that CKD is diagnosed in 40% of domestic cats older than 10 years of age (Sparkes et al., 2016). It is believed that the high mortality rate associated with CKD is due to the inability to staunch histopathological changes in the renal parenchyma, as well as to complications associated with metabolic acidosis (Chakrabarti et al., 2012; Hopper and Epstein, 2012; McLeland et al., 2015). Metabolic acidosis occurs commonly with CKD due to the retention of acids that are excreted normally by the kidneys if the glomerular filtration rate (GFR) is normal (Bartges, 2012). It is assumed that the GFR in healthy cats ranges from 1.30 to 1.40 mL/kg/min although it is rarely assessed clinically (Finch, 2014). Hence, it is often difficult to identify metabolic acidosis in the course of CKD, rendering its diagnosis and treatment impossible (De Brito-Ashurst et al., 2009; Di Iorio et al., 2012).

Previous studies in cats show that metabolic acidosis develops with the progression of CKD and is usually diagnosed at its last stage (Elliott et al., 2003; Bartges, 2012; Reynolds and Lefebvre, 2013). Human studies suggest that mild to moderate metabolic acidosis occurs in the majority of patients with CKD, which is thought to be caused by the fact that the

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concentration of the carbonate buffer (HCO_3^-) rarely decreases below 12 mmol/L (Kraut and Kurtz, 2005; Dębowska et al., 2013).

The standard diagnosis of metabolic acidosis using the Hendersson–Hasselbalch formula is based on an analysis of the elements of the carbonic acid–bicarbonate buffer system in arterial blood (in veterinary practice often in venous blood). This model includes the measurement of the pH value and the partial pressure of carbon dioxide (pCO_2) and using the calculated value of HCO_3^-. Based on the classic model, metabolic acidosis is characterised by a primary decrease in the concentration of HCO_3^- and a compensatory decrease in pCO_2 caused by an increased respiratory rate, leading to pH normalisation (Kellum, 2000). Clinical evidence suggests that changes in HCO_3^- concentration occur at such a late stage of the disease that it is futile to supplement bicarbonates and taurine orally even though they inhibit the pathologic processes in the kidneys (De Brito-Ashurst et al., 2009; Di Iorio et al., 2012; Han and Chesney, 2012). Studies performed on cats have shown that metabolic acidosis is diagnosed in advanced-stage CKD using the classic model (Elliott et al., 2003; Paepe and Daminet, 2013).

Acid–base balance (ABB) disturbances may also be diagnosed based on the serum concentration of selected ions (Na^+, K^+, Cl^-, HCO_3^-, albumins) in order to determine the anion gap (AG, i.e. the concentration of unmeasured anions), the corrected AG (AG_{corr}) which also uses the albumin concentration and the chloride/sodium ratio (Cl^-/Na^+) of the serum. Resulting from the low electroneutrality, the concept of the AG is closely related to the analysis of the ABB based on the classic model (Constable, 2000; Kraut and Madias, 2007; Morris and Low, 2008). The AG usually increases in the course of metabolic acidosis (Morris and Low, 2008). This is associated with a decreased concentration of HCO_3^- caused by a lower exploitation of the HCO_3^- buffer which binds H^+ (Smuszkiewicz and Jakieła-Sokołowska, 2011). However, a decrease in serum HCO_3^- concentration may sometimes be accompanied by a compensatory increase in the serum chloride ion (Cl^-) concentration, with the AG remaining unchanged (Kraut and Kurtz, 2005). Hence, metabolic acidosis is classified as a normal anion gap (or hyperchloraemic) metabolic acidosis or a high anion gap (or normochloraemic) metabolic acidosis (Casaletto, 2005; Emmett, 2006; Kraut and Madias, 2007). Less often, an elevated serum anion gap is caused by a laboratory error, accumulation of anionic paraproteins, metabolic alkalosis and severe hyperphosphataemia (Kraut and Madias, 2007). Studies in dogs and cats have shown that the AG value increases in about 30% of patients with diagnosed metabolic acidosis (Hopper et al., 2014b). It has also been found that the AG value may decrease in cats with advanced-stage CKD (Paepe and Daminet, 2013).

The AG value does not take into account the concentration of the blood protein (especially albumin) buffer, which should be considered in the assessment of metabolic acid–base disorders, as the serum albumin concentration often decreases in the course of such disorders. Hence, the corrected AG (AG_{corr}) is calculated in the clinical practice, as it takes into account the AG with relation to the patient's current serum albumin concentration (Morgan, 2009; Smuszkiewicz and Jakieła-Sokołowska, 2011). Some authors claim that the AG has no diagnostic value without this correction (Feldman et al., 2005).

The ABB of an organism can also be described by the Stewart model (Strong Ion Approach), which assumes that body water is the most important and inexhaustible source of hydrogen ions that form from the dissociation of water. Hence, plasma pH changes result entirely from a change in the degree of water dissociation, affected not only by pCO_2, albumin and phosphate but also by the difference in the concentration of fully dissociated ions, i.e. the strong ion difference (SID) (Morgan, 2009). This, in turn, is determined by the concentration of Na^+ and Cl^- (Stewart, 1978, 1983; Constable, 2000). This assumption is used to rapidly diagnose ABB based on the blood chloride/sodium ratio (Cl^-/Na^+), assuming that the blood serum concentration of the remaining fully dissociated ions is relatively low compared with that of Na^+ and Cl^- in a human study (Kraut and Madias, 2007; Morgan, 2009). Values below 0.75 indicate alkalosis, while those above 0.80 indicate acidosis (Fencl et al., 2000). Goggs et al. (2017) and Vanova-Uhrikova et al. (2017) also supported this idea in their experiment on dogs and cats. The diagnostic criteria for metabolic acidosis used in this study are presented in Table 1.

Symmetric dimethylarginine (SDMA) has been shown to be an accurate and precise biomarker for calculating estimated GFR in humans, as well as a more sensitive biomarker than creatinine for assessing renal dysfunction (Hall et al., 2014). The concentration of SDMA in feline blood is frequently used as an endogenous surrogate marker in research studies as well as in the clinical practice. This is due to the fact that the concentration of SDMA in the blood (unlike that of creatinine) is independent of the animal's muscle mass and age, and does not correlate with the lean body mass (Hall et al., 2014; Hokamp and Nabity, 2016).

The aim of this study was to carry out a comparative analysis of the utility of the classic model, AG, AG_{corr} and the Cl^-/Na^+ ratio in the diagnosis of acid–base disorders in cats with CKD.

MATERIALS AND METHODS

This retrospective study was carried out on 100 neutered cats of different breeds (74 European Shorthair, 10 Persian, 6 British Shorthair, 4 Siamese cat, 3 Devon Rex, 3 Maine Coon) of both sexes (64 males, 46 females) from seven to nine years old (mean = 8.1, SD = 0.75), with a body weight from 2.5 to 9.2 kg (mean = 4.37, SD = 1.08). The control group (Group C) consisted of 20 healthy, neutered cats with normal serum creatinine, SDMA and urea concentrations. The study group consisted of 80 neutered domestic cats of both sexes from seven to nine years old, which were

Table 1. Diagnostic criteria for metabolic acidosis for the traditional and Stewart's acid–base analysis

Diagnostic criteria for metabolic acidosis			
Classic model		Stewart's analysis	
pH[a]	Usually without changes	SID	<40[b]
pCO_2[a]	Below reference ranges	Cl^-/Na^+	>0.8[c]
HCO_3^-[a]	Below reference ranges		
Metabolic acidosis associated with increased AG[b]	AG > 20 mmol/L		
Metabolic acidosis not associated with increased AG[b]	AG ≤ 20 mmol/L		

pCO_2 – partial pressure of CO_2 in arterial blood; HCO_3^- –bicarbonate concentration in arterial blood; AG = $(Na^+ + K^+) - (Cl^- - HCO_3^-)$; SID = $(Na^+ + K^+) - (Cl^-)$; $Cl^-/Na^+ = (Cl^-):(Na^+)$.
[a]According to Kellum (2000).
[b]According to Hopper et al. (2014a).
[c]According to Fencl et al. (2000).

diagnosed with CKD based on the serum concentrations of creatinine, SDMA and urea. Echocardiography, abdominal ultrasound, urinalysis and urine/protein ratio (UPC) determination were carried out in all cats to exclude acute kidney injury (AKI) and prerenal causes of azotaemia. The animals from the study group were divided into four groups based on the stage of the disease (Groups I, II, III and IV) according to the criteria adopted by the International Renal Interest Society – IRIS (Brown et al., 2016). According to the IRIS guidelines, cats with a persistent increase in SDMA above 14 µg/dL that suggested reduced renal function and/or had serum creatinine concentrations within the reference range that increased in consecutive blood analyses, were included in Group I. Each group consisted of 20 animals, and the division criteria are presented in Table 2. The serum urea concentration was used as an additional indicator of azotaemia (Table 2). Arterial and venous blood was collected from each animal. Arterial blood was collected from the femoral artery. Arterial blood was drawn into heparinised 2-mL syringes using 23 G needles and immediately transported to the laboratory for testing. The samples were transported on ice. The ABB parameters – pH, pCO_2 and arterial bicarbonate concentration ($aHCO_3^-$) – were assessed using the Osmetech OPTI CCA Blood Gas System (Table 3). Measurements were taken at 37 °C. If necessary, cats were sedated with medetomidine at 10 µg/kg s.c. prior to arterial blood collection. Eighteen cats had to be sedated. According to Congdon et al. (2013), dexmedetomidine administration does not affect the ABB parameters or the concentrations of Na^+, K^+ and Cl^- in dogs. Hence, animals that had received medetomidine were not excluded from the study group (Congdon et al., 2013). The concentrations of Na^+, K^+, Cl^-, Pi, HCO_3^- ($vHCO_3^-$), albumin, glucose, lactate, and the activity of ALT, AST and alkaline phosphatase were measured in serum samples (Konelab Prime 30ISE ABC Animal Blood). Complete blood count (CBC) was carried out from venous blood (ABC Animal Blood Counter).

Table 2. Inclusion criteria for grouping cats based on the stage of CKD in accordance with the IRIS guidelines

Criterion	Stage of CKD			
	I	II	III	IV
Azotaemia[a]	Non-azotaemic	Mild azotaemia	Moderate azotaemia	Severe azotaemia
Blood creatinine, µmol/L[a]	≤140	140–250	251–440	≥440
SDMA, µg/dL[a]	≥14	≥25	≥45	Exceeding threshold value
Blood urea, mmol/L[b]	4.8–10.1	13.1–19.9	20.3–45.5	45.7–54.0

[a]IRIS guidelines.
[b]Range obtained in the present study.

The concentration of blood SDMA was assessed using the enzyme immunoassay method (EIA method) in a reference IDEXX laboratory.

Based on the obtained results, the values of AG, AG_{corr}, Cl^-/Na^+ and SID were calculated according to the formulae provided by other authors (Kraut and Madias, 2007; Smuszkiewicz and Jakieła-Sokołowska, 2011; Vanova-Uhrikova et al., 2017):

$$\mathbf{SID} = (\mathbf{Na^+ + K^+}) - (\mathbf{Cl^-})$$

$$\mathbf{AG} = (\mathbf{Na^+ + K^+}) - (\mathbf{Cl^- - vHCO_3^-})$$

$$\mathbf{AG_{corr}} = \mathbf{AG} + (\mathbf{39 g/L - alb_{act}\ g/L})/\mathbf{4}\,,$$

where: 39 g/L was the upper normal threshold of feline serum albumin concentration and alb_{act} was the serum albumin concentration in the studied cats.

$$\mathbf{AG_{diff}} = \mathbf{AG} - \mathbf{AG_{corr}}$$

$$\mathbf{Cl^-/Na^+} = (\mathbf{Cl^-}) : (\mathbf{Na^+})$$

The mean and standard deviation were calculated for all the results. One-way analysis of variance (ANOVA) was used to compare the values of the different groups and assess the statistical differences between them. If the equal mean hypothesis was rejected, a post-hoc Tukey's Honest Significance Different (HSD) test was carried out in order to determine the statistical difference between groups. The significance level was drawn at 5% and all the analyses were carried out using the Statistica 12 software (StatSoft Poland).

The Local Ethics Committee on Animal Research in Wrocław declared in its resolution 94/2017, on October 25,

Table 3. A comparison of the mean acid–base balance parameters (with reference values) analysed in arterial blood in the control group (C) and in cats with various stages of CKD (I–IV)

Parameter	C	I	II	III	IV
pH (7.41–7.46)[a]	7.42 ± 0.04	7.42 ± 0.01	7.42 ± 0.09	7.41 ± 0.02	7.41 ± 0.08
pCO_2 mmHg (26.2–34.8)[a]	31.26 ± 1.84	30.78 ± 2.44	29.27 ± 2.07	26.85 ± 1.49	24.90 ± 1.01
$aHCO_3^-$, mmol/L (18.0–21.6)[a]	22.47 ± 2.02	20.02 ± 0.43	19.54 ± 0.42	19.33 ± 0.68	17.71 ± 0.67
n =	20	20	20	20	20

pCO_2 – partial pressure of CO_2 in arterial blood; $aHCO_3^-$ – bicarbonate concentration in arterial blood; *n* – number of cats in each group; ± – standard deviation.
[a]Reference values of Uni-Lab Veterinary Diagnostic Laboratory (DiBartola, 2006).

2017, that in accordance with Article 1, Point 2.1 of the Act on the Protection of Animals Used for Scientific or Educational Purposes from January 15, 2015, this study did not require the approval of the Committee.

RESULTS

The comparison of the mean ABB parameters in the control group and in the groups of cats with various stages of CKD is presented in Table 3. In all groups, the arterial blood pH was similar. Similar observations were made in groups I, II and III with reference to the pCO_2 and $aHCO_3^-$ values. Results in group IV show signs of mild, compensated metabolic acidosis. According to the H–H equation, none of the other animals had any ABB disorders.

The mean Na^+, K^+, Cl^-, P_i, HCO_3^- and albumin concentrations in venous blood from the studied animals are presented in Table 4. The concentration of serum ions, albumin and HCO_3^- in the control group (C) and in group I showed similar values and did not differ. The concentration of serum Na^+ in all groups was within the reference range. However, there was a significant difference in the Na^+ concentration between groups II, III and IV as well as between group I and the control group. The serum K^+ concentration in all the cats was within the reference range, and it was significantly higher in group IV than in groups I and C. The serum Cl^- concentration in groups II, III and IV exceeded the upper reference limit for felines (hyperchloraemia) and differed significantly from the concentrations recorded in groups C and I. The blood concentration of Pi in cats from groups I, II and III were within the reference range for that species and did not differ significantly from that of the control group. Despite the absence of statistically significant differences between the groups, there was a clear tendency of an increasing P_i concentration in cats of group I, II and III, i.e. corresponding to the progression of CKD according to the IRIS scale. The concentration of P_i was significantly higher in cats of group IV compared to those in the control group and in groups I, II and III (Table 4). The concentration of HCO_3^- in venous blood ($vHCO_3^-$) was also within the normal range and was significantly lower in group IV than in groups C and I. Serum albumin concentration in groups III and IV was below the feline reference range (hypoalbuminaemia) and was significantly lower than that recorded in groups C and I.

Table 5 presents the mean values of AG, AG_{corr}, AG_{diff}, Cl^-/Na^+ and SID calculated based on the ion, HCO_3^- and albumin concentration in venous blood. The values of AG in all the animals were within the reference values for cats provided by Kaae and de Morais (2008), although the values in groups II, III and IV were significantly lower than those in groups C and I. The values of AG_{corr} and SID calculated for the animals from groups C and I were similar and did not differ significantly, while they were significantly higher than in the cats from groups II, III and IV. An opposite phenomenon was observed in the case of AG_{diff} value analysis – this value was significantly lower in cats of groups C and I than in cats from groups II, III and IV.

The results of the Cl^-/Na^+ ratio were consistent with those reported by Goggs et al. (2017) in all the cats, although

Table 4. Comparison of the mean Na^+, K^+, Cl^-, HCO_3^- and albumin concentration (with mean values) in venous blood in the control group (C) and in cats with various stages of CKD (I–IV)

	C	I	II	III	IV
Na^+, mmol/L (144–156)[b]	148 ± 2.12	147 ± 3.03	154[a] ± 1.80	152[a] ± 1.34	152[a] ± 1.48
K^+, mmol/L (4.10–5.60)[b]	4.71 ± 0.42	4.67 ± 0.23	4.42 ± 0.14	4.72 ± 0.29	5.26[a] ± 0.24
Cl^-, mmol/L (102–118)[b]	106 ± 3.01	107 ± 2.28	120[a] ± 1.27	120[a] ± 0.86	121[a] ± 1.46
P_i, mmol/l (1.45–2.60)[b]	1.20 ± 0.14	1.46 ± 0.3	1.56 ± 0.16	1.57 ± 0.18	4.01 ± 1.07
$vHCO_3^-$, mmol/L (18.0–23.2)[b]	21.9 ± 0.83	21.4 ± 0.69	21.7 ± 0.42	21.4 ± 0.51	19.4[a] ± 0.66
Albumin, g/L (27–39)[b]	33 ± 3.11	32 ± 2.43	27[a] ± 2.02	24[a] ± 1.51	24[a] ± 1.51
n =	20	20	20	20	20

[a]$P < 0.001$ compared to group C and group I; $vHCO_3^-$ – bicarbonate concentration in venous blood.
[b]Reference values of Uni-Lab Veterinary Diagnostic Laboratory.

Table 5. Comparison of the mean values of SID, AG, AG_{corr}, AG_{diff} and Cl/Na in the control group (C) and in cats with various stages of CKD (I–IV)

	C	I	II	III	IV
SID	46 ± 2.16	45 ± 3.89	38[a] ± 1.48	37[a] ± 1.37	37[a] ± 1.59
AG	24.93 ± 2.92	24.03 ± 3.85	15.91[a] ± 1.43	15.47[a] ± 1.65	17.19[a] ± 1.27
AG_{corr}	26.31 ± 3.82	25.68 ± 4.17	18.89[a] ± 1.47	19.17[a] ± 1.65	20.93[a] ± 1.27
AG_{diff}	1.37 ± 0.52	1.65 ± 0.60	2.97[a] ± 0.50	3.71[a] ± 0.50	3.68[a] ± 0.37
Cl/Na	0.71 ± 0.04	0.71 ± 0.02	0.77[a] ± 0.08	0.78[a] ± 0.01	0.78[a] ± 0.01
n =	20	20	20	20	20

[a]$P < 0.001$ compared to group C and group I.

they were significantly higher in groups II, III and IV compared to the values found in groups C and I.

The results of CBC analysis of the venous blood did not vary, and all the parameters were within the reference range. Similarly, the glucose and lactate concentrations and the activities of ALT, ASP and alkaline phosphatase were within the normal limits.

DISCUSSION

The obtained results analysed in accordance with the guidelines issued for the interpretation of the classic model show that a compensated, mild metabolic acidosis was present only in group IV, as the blood concentration of pCO_2 and the arterial HCO_3^- concentration were slightly below the reference range (Kellum, 2000; Kraut and Kurtz, 2005). The present findings are consistent with those of Elliott et al. (2003), who used this model in cats and found that the features of metabolic acidosis visible in the blood examination are evident only in an advanced stage of kidney failure. Similar results were obtained by Schück and Matousovic (2005) and Kraut and Kurtz (2005), who found that the ABB parameters in some people with CKD remain unchanged despite severe kidney damage. Human studies have found that the concentration of HCO_3^- was normal or slightly decreased in almost 20% of human patients with advanced CKD (Wallia et al., 1986; Caravaca et al., 1999). The normal concentration of HCO_3^- in groups II and III most likely results from the release of carbonates by the buffer reserve from bone, which is consistent with the views of other authors (Wallia et al., 1986; Caravaca et al., 1999; Ahn et al., 2012).

Cl^- is the principal anion in the extracellular fluid. Hence, it is assumed that a decrease in plasma Cl^- increases SID causing hypochloraemic alkalosis, while an increase in plasma Cl^- often decreases SID causing hyperchloraemic acidosis (Goggs et al., 2017). Therefore, the statistically significant increase in chlorine concentration, a decrease in HCO_3^- concentration and the unchanged AG value signified hyperchloraemic (i.e. normal or low AG) metabolic acidosis in groups II, III and IV. This is consistent with the observations of Hopper and Epstein (2012), who stated that hyperchloraemic metabolic acidosis appears to be more common in cats than a high-AG metabolic acidosis. The AG values were within the reference range in all groups, although they were significantly lower in groups II, III and IV than in groups C and I, which, according to the findings of Kraut and Madias (2007), indicates the worsening of hyperchloraemic metabolic acidosis. According to Hopper et al. (2014a) and Feldman et al. (2005), a decrease in the AG value may result from a low blood albumin concentration, which was observed in the present study.

Many authors believe that AG should be corrected if it is to be used to assess metabolic disorders, i.e., its value should be adjusted to correspond to the actual concentration of albumin, a protein blood buffer, the concentration of which can rapidly decrease in the course of metabolic diseases (Figge et al., 1998; Feldman et al., 2005; Hopper and Epstein, 2012). In human medicine, the concept of a modified AG takes into account the concentration of the protein blood buffer and combines the classic model with the Stewart model (Fencl et al., 2000). Due to the fact that there are no other reports of AG_{corr} values in cats, the current results cannot be compared with those of other studies. The AG_{corr} values in group C and group I were similar to those reported in healthy dogs (Vanova-Uhrikova et al., 2017). Small differences resulted from different reference thresholds of serum albumin concentrations – 39 g/L in the present study and 29.5 g/L reported by Vanova-Uhrikova et al. (2017). The AG_{corr} values calculated in cats in groups II–IV were the same as those calculated in children (Hatherill et al., 2002), whose blood albumin levels were similar to those in the studied cats. In human medicine, it is believed that if the difference between AG and AG_{corr} exceeds 2–3, unidentified anions, associated with a worse patient prognosis, may be present (Balasubramanyan et al., 1999). In the case of renal failure, such anions usually include hippurans, which are formed intermediately in the Krebs cycle and are considered to be uraemic toxins appearing in the blood as a result of progressive impairment of glomerular filtration in the course of CKD (Vanholder et al., 2003, 2009). In the present study, the obtained difference (AG_{diff}) between the AG and AG_{corr} in groups II, III and IV amounted to 2.97, 3.71 and 3.68, respectively, which may be an indicator of the presence of uraemic toxins.

Some authors believe that the Cl^-/Na^+ ratio is a more accurate and better indicator of ABB disorders than AG (Durward et al., 2001; Goggs et al., 2017). In the case of

high-AG metabolic acidosis, Durward et al. (2001) demonstrated the usefulness of the Cl^-/Na^+ ratio, which decreased with the decrease of blood Cl^- concentrations and an increase in the AG. However, the Cl^-/Na^+ ratio does not appear to be more useful than AG in the case of hyperchloraemic metabolic acidosis. In this study, the Cl^-/Na^+ ratio was significantly higher in the cats from groups II, III and IV compared to groups C and I, supporting its usefulness in the diagnosis of hyperchloraemic metabolic acidosis. However, the values of the Cl^-/Na^+ ratio remained within the range provided by Goggs et al. (2017) in all the groups (0.74–0.80), including group IV diagnosed with metabolic acidosis based on the Henderson–Hasselbalch equation (HH equation). Based on this study, the upper reference range of the Cl^-/Na^+ ratio in cats with suspected CKD should approximate 0.77–0.78. This is supported by the findings of the Cl^-/Na^+ ratio in the cats from groups II and III, which were diagnosed with hyperchloraemic metabolic acidosis based on the AG, the AG_{corr} and the difference between those two values. Moreover, the SID value was decreased in cats from groups II, III and IV, which, according to the Stewart model, clearly indicates metabolic acidosis both in humans (Durward et al., 2001; McCullough and Constable, 2003; Corey, 2005) and cats (Hopper et al., 2014a). Based on their results, the authors of this study concluded that an analysis of the changes in SID and AG is more precise, reliable and simpler in the diagnosis of metabolic acidosis than the classic model. This is supported by the results of Hopper et al. (2014a), who compared three methods of acid–base analysis in dogs and cats and found greater diagnostic utility of the method based on the Stewart model. Our findings are consistent with the conclusions of Morgan (2009), who claimed that the diagnosis of ABB disorders in the course of kidney failure should be based primarily on the Stewart model.

Contrary to the findings of Elliott et al. (2003), a significant increase in the blood concentration of Cl^- with an increase in the stage of CKD was seen in this study. However, this result is consistent with the findings of Hopper and Epstein (2012), who observed hyperchloraemia in 37% of cats with diagnosed metabolic acidosis. Hopper and Epstein (2012) defined hyperchloraemia as an increase in blood Cl^- concentration above 124 mmol/L, hence above the values obtained in this study. Hypokalaemia is known to occur in 18–30% of cats with CKD (Elliott and Barber, 1998; Elliott et al., 2003; Reynolds and Lefebvre, 2013; Bartges, 2012). This phenomenon was not observed in our results, although a significant increase in serum K^+ concentration was seen in the cats of group IV. This is consistent with the findings of other authors, who noted an increased K^+ concentration in the same stage of CKD, owing to reduced potassium excretion (Elliott and Barber, 1998; Elliott et al., 2003; Paepe and Daminet, 2013).

According to the authors, the changes in ion concentration in the course of CKD require further analysis. They may be dependent on the site of nephron damage and may also be associated with the presence, severity or absence of vomiting.

Based on the obtained results we can conclude that ABB analysis using the classic model enabled the detection of ABB disorders in cats in IRIS stage IV of CKD. However, the analysis of the AG, AG_{corr} and AG_{diff} values allow us to diagnose ABB disorders even in cats in IRIS stages II and III of CKD. The analysis of concentration changes in the course of CKD is a more precise tool for the detection of ABB than the classic model. Our results suggest that the blood ion concentrations should be monitored regularly in cats diagnosed with stage I of CKD based on SDMA concentration in order to analyse the AG, AG_{corr}, AG_{diff} and Cl^-/Na^+ ratio. This may allow early diagnosis of ABB disorders and the implementation of an effective therapy. Further research on this topic is warranted.

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