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Original article

An attempt to use the serum concentration of the phosphate (P_i) and the Ca x P product as markers of the progression of chronic kidney disease in cats

P. Sławuta, E. Kumiega, A. Sikorska-Kopyłowicz, G. Sapikowski, A. Kurosad

Department of Internal Diseases with Clinic for Horses, Dogs and Cats, Faculty of Veterinary Medicine, Wroclaw University of Environmental and Life Sciences, pl. Grunwaldzki 47, 50-366 Wrocław, Poland

Abstract

The aim of this study was to determine whether the serum concentration of the phosphate (P_i) and the Ca x P value correlate with the IRIS stage of chronic kidney disease (CKD) in cats and, thus, whether they can be used as markers of the disease progression. Another aim was to assess whether the concentration of Ca in blood needs to be corrected based on the albumin concentration. The study was performed on 165 cats divided into five groups: the healthy group – C and study groups: I, II, III and IV with cats assigned to the groups based on the IRIS scale. Blood was collected from all the animals. The product of Ca x P_i, Ca_{corr} and the product of Ca_{corr} x P_i were calculated based on the obtained results. Despite no differences between groups I-III, there was a clear upward trend in the P_i concentration, in the Ca x P_i and in the Ca_{corr} x P_i with CKD progression. In group IV, the P_i concentration and the Ca x P_i as well as the Ca_{corr} x P_i value were significantly higher than the other groups. The concentration of Ca and its albumin-corrected serum values did not differ significantly. The serum concentration of P_i and the Ca x P product cannot be used as indicators of CKD progression in cats, but they may be used as additional elements in the diagnosis of stage IV CKD. The results also suggest that the serum calcium concentrations do not need to be albumin-corrected in cats.

Key words: chronic kidney disease (CKD), serum phosphate concentration, serum Ca x P product, cats

Introduction

Chronic kidney disease (CKD) is defined as a sustained decrease in renal function lasting longer than three months that is highly prevalent in domestic cats (Sparkes et al. 2016). Novel risk factors for development of CKD in cats are frequently reported (Finch et al. 2016). It is well known that the GFR is the best indicator of the kidney status and function, yet its measurement in clinical practice in cats is challenging (Chakrabarti et al. 2012). Hence, the detection of specific and sensitive markers of kidney damage, which are also

Correspondence to: P. Sławuta, e-mail: piotr.slawuta@upwr.edu.pl

surrogate markers of GFR, is particularly significant in cats as it enables an early detection of CKD and the implementation of treatment that may constrain disease progression (Finch et al. 2018). Studies of changes in serum ion concentrations, which result from CKD progression, are becoming increasingly common (King et al. 2007, Chakrabarti et al. 2013, Nadkarni and Uribarri 2014, Felsenfeld et al. 2015, Finch et al. 2018). Hyperphosphatemia almost always occurs in the course of CKD, which stimulates secretion of the parathyroid hormone (PTH) as the disease progresses, causing secondary renal hyperparathyroidism (SRHP) (Barber and Elliott 1998, Kestenbaum et al. 2005, Young et al. 2005, Schropp and Kovacic 2006, Boyd et al. 2008, Kidder and Chew 2009, Polzin 2011, Chakrabarti et al. 2012). Phosphorus homeostasis is not completely understood although it is known to be regulated by the gut, bone and parathyroid glands (Geddes et al. 2013a). It is also assumed that, in some simplification, it is dependent on the P dietary intake and its renal excretion (Schropp and Kovacic 2006, Polzin 2011, Nadkarni and Uribarri 2014, Felsenfeld et al. 2015). In the healthy kidney, phosphate ions are freely filtered at the glomerulus. If plasma inorganic phosphate (P_i) concentrations fall below approximately 1mmol/l (3.1 mg/dl), all of the P_i ions in the glomerular filtrate are reabsorbed (Geddes et al. 2013a,b). At an early stage of kidney disease, a balance is maintained between phosphorus gastrointestinal absorption and its excretion in urine (Geddes et al. 2013a, Felsenfeld et al. 2015). The amount of filtered phosphorus decreases with the decrease of the glomerular filtration rate (GFR) as does the amount of filtered P_i. At the same time, its reverse absorption in the proximal tubule decreases, and it is assumed that an increase in the P_i concentration by a mg/dl above the reference value signifies a decrease in the GFR by 0.154 ml/min (Voormolen et al. 2007). In humans, if the GFR is below 30 ml/min/1.73 m^2, adaptive mechanisms can no longer maintain the serum P_i in the normal range, and an imbalance in the phosphate intake and renal excretory capacity occurs (Felsenfeld et al. 2015). High plasma P_i is an independent risk factor for a more rapid decline in the renal function (King et al. 2007, Voormolen et al. 2007). Because phosphate is freely filtered at the glomerulus, the plasma Pi concentration can be considered as a marker of the GFR (Barber and Elliott 1998, Chakrabarti et al. 2012, Chakrabarti et al. 2013). In cats with CKD, there is an increase in the blood P_i concentration (Barber and Elliott 1998, Kidder and Chew 2009, Geddes et al. 2013a) and this may be an indicator of the renal survival time (King et al. 2007). The International Renal Interest Society (IRIS) has developed recommendations concerning the maximal serum P_i concentration in cats with various stages of CKD (Kidder and Chew 2009, Geddes et al. 2013a, Polzin 2013, Quimby and Lappin 2016), although it is unclear whether there is a correlation between an increase in the serum P_i concentration and the IRIS stage of CKD, or whether this potential increase is significant enough to serve as a reliable indicator of the stage of CKD.

One of the indicators describing the calcium and phosphate metabolism is the calcium-phosphate product (Ca x P). In clinical practice, it is used to diagnose metastatic calcifications and to determine the risk of death in people with CKD (Block at al. 1998, Goodman et al. 2000, McCullough and Soman 2004, Voormolen et al. 2007). In human medicine, according to the recommendations of the Kidney Disease Outcome Quality Initiative (K/DOQI) , the Ca x P product should range from 42 to 52 mg^2ml^2, while CaxP values exceeding 72 mg^2/dl^2 are associated with an increased risk of death (Block et al. 1998, Ganesh et al. 2001 , Kidder and Chew 2009). In veterinary medicine, there are no studies or recommendations concerning this indicator. The only available data states that Ca x P values above 70 mg^2ml^2 may cause metastatic calcifications in dogs (Schaer et al. 2001) and cats (Jackson and Barber 1998, Bertazzolo et al. 2003). It is currently unclear whether there is a correlation between the Ca x P value and the IRIS stage of CKD in cats. However, based on studies in humans (Block et al. 1998, Voormolen et al. 2007), Ca x P may be a valuable marker of CKD progression in cats. In humans with hypoalbuminemia, and assuming that 1 gram of albumin binds approximately 0.8 mg (0.2 mmol) of Ca (Voormolen et al. 2007), the serum concentration of Ca is corrected using the following formula:

Corrected calcium (Ca_{corr}) = calcium, if serum albumin ≥ 40g/l, and Ca_{corr} = calcium (mg/dl) + 0,08 x (40 – serum albumin g/l), where 40 is the median of the normal range of the albumin concentration in humans, expressed as g/l (Block et al. 1998). It is uncertain whether the Ca concentration in cats with CKD needs to be albumin-corrected. This seems to be particulary important as cats with CKD frequently receive a low--phosphorus, low-protein diet and are often anorexic, which may lead to hypoalbuminemia (White et al. 2011, Hall et al. 2019).

Aim

The aim of this study was to determine whether the serum P_i concentration and the Ca x P value correlate with the IRIS stage of CKD in cats, and whether they may be used as indicators of CKD progression. In addition, we aimed to determine whether it is necessary to adjust the Ca serum concentration depending on the serum albumin concentration in cats with CKD.

Table 1. Criteria used to divide the cats into four groups based on the stage of CKD in accordance with IRIS guidelines* (measured twice), and the urea concentration measured twice in all the animals**.

	Stage of CKD		
Criterion	I	II	III
Azotaemia*	Non-azotaemic	Mild azotaemia	Moderate azotaemia
Blood creatinine µmol/l *	Below 140	140-250	251-440
SDMA µg/dl *	Above 14	Above 25	Above 45
Blood urea mmol/l **	4.8-10.1	13.1-19.9	20.3-45.5

* IRIS guidelines, ** range obtained in present study

Table 2. Comparison of the mean values of SDMA, blood creatinine concentration and blood urea concentration in the control group and in cats with various stages of CKD.

	C	I	II	III	IV
SDMA µg/dl	4.24 ± 1.55	18.42* ± 1,79	32.36* ± 3.53	46.21* ± 2.83	49.66* ± 0.97
Blood creatinine µmol/l	76.75 ± 12.7	123.00* ± 8.14	182.84* ± 18.14	307.36* ± 20.38	980.24* ± 37.19
Blood urea mmol/l	7.1 ± 1.11	7.91 ± 1.51	15.52* ± 2.79	32.71* ± 2.72	47.00* ± 6.88
n =	33	33	33	33	33

SDMA – serum SDMA concentration, Blood creatinine – serum creatinine concentration, Blood urea – serum urea concentration
C – control group, I – cats with stage I CKD, according to the IRIS scale, II – cats with stage II CKD, according to the IRIS scale, III – cats with stage III CKD, according to the IRIS scale, IV – cats with stage IV CKD, according to the IRIS scale
* $p<0,001$, n – number of cats in each group, ± – standard deviation

Materials and Methods

The study was performed on 165 castrated domestic cats of both sexes from 7 to 9 years old. An anamnesis was collected from the cat-owners, while a clinical examination, echocardiography, urinalysis with UPC, CBC (RBC, WBC, HGB, HCT) and blood biochemistry were performed on all the cats. Venous blood was then collected from each cat and the concentration of symmetric dimethylarginine (SDMA), Ca, P_i, albumin, creatinine, urea, the activity of ALT, AST and alkaline phosphatase were measured. SDMA in blood was assessed using the EIA method in a reference IDEXX laboratory using an AU5800 Beckman Coulter analyser. The biochemical blood parameters were examined using a Konelab Prime 30 ISE Thermo Scientific biochemical analyser, while haematological assessment of venous blood was carried out using an Animal Blood Counter abc™ unit. The analytical laboratory that carried out the analyses is recognised as an internationally acclaimed Quality Research Diagnostic Laboratory and participates in everyday external StandLab quality control. The control group (marked in the tables as group C) consisted of 33 healthy castrated cats of both sexes with normal serum concentrations of creatinine, SDMA and urea. The study group included 132 castrated cats of both sexes from 7 to 9 years old that were diagnosed with CKD based on the creatinine and SDMA serum concentrations. In those animals, extrarenal causes of CKD were excluded based on both the anamnesis and clinical examination. According to a previously described methodology (Finch et al. 2012), the serum urea concentration was considered an additional marker of azotemia. The animals in the study group were divided into subgroups (marked in the tables as I, II, III and IV) depending on the stage of CKD according to the IRIS scale (King et al. 2007, Brown et al. 2016), and the division criteria are presented in Table 1. Each subgroup contained 33 cats (Table 2). The adopted experimental model was consistent with those used by other authors (King et al. 2007). Based on the obtained results, the following were calculated: Ca x P_i product, Ca_{corr} and Ca_{corr} x P_i product according to the following formulae:

$$\text{Ca x } P_i \text{ product} = \text{Ca mg/dl x } P_i\text{mg/dl}$$

Ca_{corr} = Ca mg/dl + 0.08 x (33 – serum albumin g/l), where 33 was the median value of reference value for albumin in cats, expressed as g/l (Winnicka 1997). A similar formula was used by Kogika et al. (2006), to correct the calcium concentration in dogs.

$$Ca_{corr} \text{ x } P_i \text{ product} = Ca_{corr} \text{ x } P_i \text{ mg/dl.}$$

The second part of the study assessed the necessity to correct the blood Ca value in dogs depending on the serum albumin concentration. All the studied cats were divided into 13 groups depending on their serum albu-

Table 3. Comparison of mean values of P_i, Ca as well as Ca x P and Ca_{corr} x P in the control group and in cats with various stages of CKD.

	C	I	II	III	IV
P_i mg/dl	3.72 ±0.46	4.53 ±0.93	4.85 ±0.51	4.87 ±0.81	12.43* ±3.33
Ca mg/dl	9,37 ±0.76	10,08 ±0.55	10.42 ±0.43	10.44 ±0.91	11.18 ±0.78
Ca x P mg^2/dl^2	34.93±5.03	47.39±10.39	49.03±0.04	51.06±10.79	138.81*±35.09
Ca_{corr} x P mg^2/dl^2	35.59 ±4.79	48.43 ±10.51	49.97 ±6.26	51.83 ±11.63	144.4* ±36.47
n =	33	33	33	33	33

P_i – serum phosphate concentration, Ca – blood serum total calcium, Ca x P – calcium x posphate product in blood serum
Ca_{corr} x P – $calcium_{corr}$ x posphate product in blood serum, C – control group
I – cats with stage I CKD, according to the IRIS scale, II – cats with stage II CKD, according to the IRIS scale
III – cats with stage III CKD, according to the IRIS scale, IV – cats with stage IV CKD, according to the IRIS scale
* p<0,001, n – number of cats in each group, ± standard deviation

Table 4. Comparison of mean Ca and Ca_{corr} concentrations depending on blood albumin concentrations.

Group	Alb g/l	Ca mg/dl	Ca_{corr} mg/dl	± SD	n =
1	24	10,6	11,32	0,32	11
2	25	10.98	11.62	1.27	13
3	26	10.97	11.53	1.03	13
4	27	10.44	10.92	0.6	12
5	28	10.49	10.89	1.00	13
6	29	10.26	10.43	0.76	12
7	30	10.07	10.31	0.77	12
8	31	10.22	10.38	0.6	12
9	32	10.29	10.37	1.00	11
10	33	10.13	10.13	0.73	13
11	34	10.46	10.38	1.31	13
12	35	9.58	9.42	0.94	14
13	36	11.24	11.00	0.97	16

Alb – blood serum albumin concentration, Ca – total serum calcium concentration at a given serum albumin concentration
Ca_{corr} – albumin-corrected serum calcium concentration, n – number of cats in each group, ± – standard deviation

min concentration. The Ca and Ca_{corr} values were then calculated in each group.

Due to the fact that most cited studies reported the ion concentrations in mg/dl, the same units were used in this study. The obtained results underwent statistical analysis using StatSoft, Inc., 2011 STATISTICA 12 software. The mean and standard deviation were calculated. One way analysis of variance (ANOVA) was applied to assess statistically significant differences between the groups. In cases when the null hypothesis was rejected, a *post-hoc* Duncan test was applied to determine which groups differed significantly. In resolution no. 94/2017 from 25.10.2017, the Local Ethics Committee adjudicated that according to art.1 clause 2.1 of the Animal Welfare Act from January 15th 2015, concerning the use of animals for education and scientific purposes, the studies and activities carried out in the present study do not require its permission.

Results

The blood concentration of P_i and Ca in cats from groups I, II and III were within the reference range for that species and did not differ significantly from the control group (group C) - Table 3. Similar results were obtained when the Ca x P_i and Ca_{corr} x P were compared in groups I, II and III. Despite no statistically significant differences between the groups, there was a clear tendency of an increasing P_i concentration and increasing values of Ca x P_i as well as Ca_{corr} x P in cats in group I, II and III, i.e. corresponding to the advancement of CKD according to the IRIS scale. The concen-

tration of P_i and the value of Ca x P_i as well as Ca_{corr} x P_i were significantly higher in cats in group IV compared to those in the control group and in groups I, II and III – Table 3.

The concentration of Ca and the value of Ca_{corr} did not differ significantly between any of the 13 groups (Table 4).

Discussion

The value of the blood P_i and Ca concentration in cats with CKD were consistent with those of other authors (Barber and Elliot 1998, King et al. 2007, Chakrabarti et al. 2012, Finch et al. 2012). The applied experimental model was similar to that used by King et al. (2007), who studied the relationship between the concentration of creatinine, urea and P_i in blood and the renal survival time. According to King et al. (2007), the concentration of P_i in blood increases with the progression of CKD. However, regardless of the stage of the disease, the increase was not statistically significant. An increase in the P_i blood concentration of cats with the CKD progression was also described by Finch et al. (2012), although they did not use the IRIS scale but divided the cats into three groups depending on the creatinine concentration, urine specific gravity (USG) and clinical symptoms. In the presented study, a non-significant increase in the concentration of P_i was also observed in groups I, II and III. However, in contrast to the study of King et al. (2007), a significant increase in the P_i concentration was observed in group IV compared to the remaining groups of cats, which is consistent with the findings of Barber and Elliott (1998). Barber and Elliott (1998) did not classify sick cats based on the IRIS scale but divided them based on the anamnesis and clinical symptoms into three groups. The first group consisted of cats without clinical symptoms of CKD, with increased blood serum creatinine concentrations (above 180 µmol/l) classified as having "compensated" CKD. Cats in the second group and with clinical symptoms of an uraemic syndrome were classified as "uraemic". The third group was called the "end stage" group and consisted of extremely dehydrated animals that died within 21 days of the diagnosis of CKD. Barber and Elliot (1998) found a significant increase in the concentration of P_i in the blood of "uraemic" and "end stage" cats compared to healthy cats. Hence, those results are consistent with the present study as the mean serum creatinine concentration in the "uraemic" and "end stage" groups were 316 µmol/l and 909 µmol/l respectively, and in the present study such cats were predominantly classified as group IV, where the Pi concentration was significantly higher than in the remaining study groups. Previous studies suggested a strong relationship between the Pi blood concentration and the stage of CKD (Barber and Elliott 1998, King et al. 2007, Chakrabarti et al. 2012, Finch et al. 2012). However, based on the results of the present study, the P_i concentration should not be used as an indicator of CKD progression, determined using the IRIS scale. The serum Ca concentration in cats with CKD did not differ significantly with the CKD progression, which is in accordance with other studies (Barber and Elliott 1998, King et al. 2007, Finch et al. 2012). The observed non-significant increase in the Ca x P value in groups I, II and III of cats with progression of CKD is also consistent with other studies (Finch et al. 2012). The acquired Ca x P values were somewhat higher than those reported by Finch et al. (2012), although this is most likely due to differences in group classification. Despite the fact that the blood concentration of Ca in cats in group IV did not differ significantly from the remaining animals, the Ca x P value was significantly higher in this group. This may indicate the applicability of this parameter in the diagnosis of stage IV CKD in cats. This is also confirmed by other authors. According to Finch et al. (2012), the value of Ca x P does not change in non-azotemic cats, while the results of Bertazzolo et al. (2003) suggest that the Ca x P value in this species increases regardless of the blood urea and creatinine concentration. These results also suggest that the Ca value in cats does not have to be albumin-corrected. In order to confirm this finding, further research is warranted as the cats in this study had different fractions of this protein (Table 4). The obtained results cannot be compared to those obtained by other authors as the literature review suggests that similar studies have not been previously performed in cats. To date, the serum Ca concentration in cats has been corrected using canine albumin values (Kogika et al. 2006) although the authors do not provide non-corrected and corrected Ca concentrations.

Conclusions

Based on this study, the serum P_i concentration and the Ca x P product cannot be used as markers of CKD progression in cats although they may be used as additional elements in the diagnosis of stage IV CKD according to the IRIS scale. The Ca x P value, which correlates with an increased risk of death in cats, may be clinically useful and warrants further research. The obtained results suggest that in cats, the serum concentration of calcium does not have to be albumin-corrected.

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