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

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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 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...
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, Chakrabarti et al. 2013, Pi concentration can be considered as a marker of the phosphate is freely filtered at the glomerulus, the plasma Pi 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 Pi 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 et 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 mg²/dl², while CaP values exceeding 72 mg²/dl² 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 mg²/dl² 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 hyperalbuminemia, 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 (Ca₉¼corr) = calcium, if serum albumin ≥ 40 g/l, and Ca₉¼corr = 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 particularly important as cats with CKD frequently receive a low-phosphorus, low-protein diet and are often anorexic, which may lead to hyperalbuminemia (White et al. 2011, Hall et al. 2019).

**Aim**

The aim of this study was to determine whether the serum Pi 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**.

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

* 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.

<table>
<thead>
<tr>
<th>C</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMA µg/dl</td>
<td>4.24 ± 1.55</td>
<td>18.42* ± 1.79</td>
<td>32.36* ± 3.53</td>
<td>46.21* ± 2.83</td>
</tr>
<tr>
<td>Blood creatinine μmol/l</td>
<td>76.75 ± 12.7</td>
<td>123.00* ± 8.14</td>
<td>182.84* ± 18.14</td>
<td>307.36* ± 20.38</td>
</tr>
<tr>
<td>Blood urea mmol/l</td>
<td>7.1 ± 1.11</td>
<td>7.91 ± 1.51</td>
<td>15.52* ± 2.79</td>
<td>32.71* ± 2.72</td>
</tr>
<tr>
<td>n =</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

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, 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 × P product, $Ca_{corr}$ and $Ca_{corr} \times P_i$ product according to the following formulae:

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

$$Ca_{corr} = Ca \text{ mg/dl} + 0.08 \times (33 – \text{ serum albumin g/l})$$

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.

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

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 alb-
min concentration. The Ca and Ca\textsubscript{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\textsubscript{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\textsubscript{i} and Ca\textsubscript{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\textsubscript{i} concentration and increasing values of Ca x P\textsubscript{i} as well as Ca\textsubscript{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, and the value of Ca x P, as well as Ca\textsubscript{corr} x P, 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\textsubscript{corr} did not differ significantly between any of the 13 groups (Table 4).

**Discussion**

The value of the blood P, 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 in blood and the renal survival time. According to King et al. (2007), the concentration of P, 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, 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, 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, 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 Elliott (1998) found a significant increase in the concentration of P, 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, 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, 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.
References


