A case-control study of the effects of nephrolithiasis in cats with chronic kidney disease

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Objective—To determine whether nephrolithiasis was associated with an increase in mortality rate or in the rate of disease progression in cats with naturally occurring stage 2 (mild) or 3 (moderate) chronic kidney disease.

Design—Retrospective case-control study.

Animals—14 cats with stage 2 (mild) or 3 (moderate) chronic kidney disease (7 with nephroliths and 7 without).

Procedures—All cats were evaluated every 3 months for up to 24 months. Possible associations between nephrolithiasis and clinicopathologic abnormalities, incidence of uremic crises, death secondary to renal causes, and death secondary to any cause were evaluated.

Results—There were no clinically important differences in biochemical, hematologic, or urinalysis variables between cats with and without nephroliths at baseline or after 12 and 24 months of monitoring. No associations were detected between nephrolithiasis and rate of disease progression, incidence of uremic crises, or death.

Conclusions and Clinical Relevance—Results suggested that in cats with mild or moderate chronic kidney disease, nephrolithiasis was not associated with an increase in mortality rate or in the rate of disease progression. Findings support recommendations that cats with severe kidney disease and nephrolithiasis be managed without surgery. (J Am Vet Med Assoc 2007;230:1854–1859)

Prior to the late 1990s, there were few reports of uroliths involving the upper urinary tract (ie, kidneys and ureters) in cats. A recent study, however, found that between 1980 and 1999, there was a 10-fold increase in the frequency of upper urinary tract uroliths among cats evaluated at 9 veterinary teaching hospitals in the United States. At the same time, authors of other recent reports have described acute ureteral obstruction as an emerging clinical syndrome in cats.

As with nephrolithiasis, the frequency of CKD in cats appears to be increasing. During 1990, for instance, the hospital proportional morbidity rate for renal failure among cats of all ages reported to the Veterinary Medical Database was 16 cases for every 1,000 cats examined. By 2000, this rate had increased to 96 cases for every 1,000 cats examined.

These observed increases in the incidences of nephrolithiasis and CKD in cats raise questions as to the potential relationship between these 2 conditions. From 1998 through 2003, we evaluated 88 cats determined on the basis of well-defined criteria to have CKD for possible inclusion in a clinical trial and found that 41 (47%) had upper urinary tract uroliths. At that time, we were unable to find any explanation for a possible association between formation of nephroliths and development of CKD, and it is currently unknown whether CKD promotes the formation of nephroliths, nephroliths contribute to the development of CKD, or the 2 conditions develop independently as sequelae of a common cause.

Importantly, the most appropriate treatment for cats with nephrolithiasis is currently unclear. Most nephroliths in cats are composed of calcium salts and, therefore, are not amenable to medical dissolution. On the other hand, given the technical demands of and high morbidity and mortality rates associated with surgical removal of nephroliths, surgical treatment may not be the best option for initial treatment either. During the past 10 years, it has been our experience that most nephroliths do not cause substantial clinical problems in cats, and we have therefore recommended the use of medical management designed to limit the size and number of nephroliths in cats with nephrolithiasis. However, the long-term clinical course of cats with concurrent nephrolithiasis and CKD is not known.

The purposes of the study reported here, therefore, were to determine the long-term clinical course of cats...
with concurrent nephrolithiasis and CKD and to compare clinical course in cats with CKD that did or did not have nephrolithiasis. Our objective was to determine whether nephrolithiasis was associated with an increase in mortality rate or disease progression in cats with naturally occurring CKD.

Materials and Methods

Case and control selection—Forty-five cats with stage 2 or 3 CKD that had been recruited from the Minneapolis–Saint Paul metropolitan area for inclusion in a 24-month-long randomized controlled trial8 of the efficacy of dietary modification in the management of CKD were considered for inclusion in the present study (Appendix). Cats had been eligible for inclusion in the previous study if, at the time of enrollment, they were > 1 year old, had a serum creatinine concentration between 2.1 and 4.5 mg/dL, and had stable stage 2 or 3 CKD for at least 4 weeks (ie, serum creatinine concentration did not increase or decrease by > 20% within 7 to 21 days after determination of the initial concentration). Cats that had been excluded from the previous study if they could be expected to die from nonrenal illness before the completion of the study; had diabetes mellitus, hyperthyroidism, overt signs of uremia (eg, anorexia, vomiting, or lethargy), or radiographic evidence of ureteroliths; were being treated with corticosteroids, H2-blocking drugs, antiemetic drugs, antihypertensive drugs, vitamin supplements, phosphate binders, alkalizing agents, potassium supplements, recombinant human erythropoietin, or vitamin D supplements; or were receiving parenterally administered fluids. Cats enrolled in the previous study were randomly assigned to be fed a standard maintenance diet or a diet modified for cats with kidney disease2 and were reevaluated every 3 months for 24 months or until they reached one of the study end points (ie, development of a uremic crisis, death as a result of renal disease, or death from any cause). After the initial 24 months of the study, cats were reevaluated intermittently (ie, every 3 to 12 months) for up to 72 months. Twelve of the 45 cats enrolled in the previous study8 had radiographic evidence of nephroliths at the time of enrollment. In 7 of these 12 cats, nephroliths had been periodically reevaluated by means of survey radiography or necropsy during the previous study, and these 7 cats were selected as case cats for the present study. Mean ± SD age of the 7 case cats was 11.6 ± 3.4 years. There were 4 neutered males and 3 spayed females. Six were domestic shorthairs, and 1 was a Siamese. Four case and 4 control cats were fed the maintenance diet, and 3 case and 3 control cats were fed the renal diet.

Study protocol—All cats had been evaluated at the time of enrollment in the previous study8 and periodically throughout the course of the study. Evaluations that were performed and the schedule for these evaluations have been described previously.8

For the present study, medical records for the 7 case and 7 control cats were reviewed, and results of clinical evaluations and laboratory testing performed at the time of enrollment and after 12 and 24 months were obtained. Information was also obtained on whether cats had developed a uremic crisis and, for cats that had died, the cause of death. Cats were considered to have developed a uremic crisis if the owner had observed at least 2 clinical signs consistent with uremia (ie, signs of depression, lethargy, anorexia, vomiting, uriniferous breath odor, or uremic stomatitis), serum creatinine concentration was at least 20% greater than the previously determined value, and no other plausible alternative for the clinical signs could be identified. For cats that died, the cause of death was classified as definitely not renal, possibly renal, probably renal, or definitely renal. Cats in which the cause of death was classified as definitely not renal or possibly renal were considered to have died from nonrenal causes. Cats in which cause of death was classified as probably or definitely renal were considered to have died from renal causes. Owner consent for necropsy was requested for all cats that died. Nephroliths that were recovered were submitted to the Minnesota Urolith Center for quantitative analysis.

Statistical analysis—After checking normality and equality of variance, 2 independent-sample t tests were used to compare baseline values for clinical and laboratory evaluations between case and control cats, and repeated-measures ANOVA9 was used to compare values obtained after 12 and 24 months between groups. The Kaplan-Meier method was used to estimate times to development of a uremic crisis or death, and the Mantel-Cox log-rank method10 was used to compare survival curves between cats with and without nephroliths (ie, case and control cats). The Cox proportional hazard regression model was used to evaluate the effects of nephrolithiasis on the odds of developing a uremic crisis, dying of renal causes, or dying of any cause. The possible association between nephrolithiasis and progression of CKD was determined by calculating, for each sampling period (ie, the time of study enrollment and every 3 months thereafter), the mean of the reciprocal of serum creatinine concentration for cats with and without nephroliths. For each group, a best-fit line was then calculated by use of the least-square method to evaluate the change in renal function.9,11 A test for parallelism of 2 regression lines12 was used to determine whether the change in the reciprocal of serum creatinine concentration was the same for the 2 groups. Data obtained at the time of a uremic crisis were not included in these analyses.

All analyses were performed with standard software.8 For all analyses, values of P < 0.05 were considered significant.

Results

Clinical and laboratory evaluations—Results of clinical and laboratory evaluations performed at the time of study enrollment were not significantly different between case and control cats (Table 1), except that...
mean urine protein-to-urate creatinine ratio was significantly higher in cats with nephroliths than in cats without. Similarly, results were not significantly different between groups after 12 and 24 months, except that after 12 months in the study, mean serum calcium concentration was significantly higher in cats with nephroliths than in cats without.

Crystalluria was observed in urine samples from 2 cats with nephroliths. In one of these cats, occasional amorphous crystals were observed in the urine sediment at the time of study enrollment, but crystals were not seen in subsequent urine samples from this cat. In the other cat, calcium oxalate monohydrate and urate crystals were observed in the urine sediment after 9 months. Generalized lymphadenopathy secondary to stage IV-B lymphosarcoma was detected at the same time; this cat died after 3 days. The control cat developed a sustained increase in serum creatinine concentration, and was euthanized after 3.2 months later because of progressive disease.

**Association between nephrolithiasis and development of a uremic crisis**—During the study, 1 case and 1 control cat developed uremic crises. The case cat developed a sustained increase in serum creatinine concentration after 43 months, did not respond to medical treatment, and was euthanized after 3 days. The control cat developed an episode of uremia after 22.6 months and initially responded to treatment, but was euthanized 3.2 months later because of progressive uremia. The proportion of cats that developed a uremic crisis was not significantly (P = 0.957; OR, 1.08; 95% CI, 0.07 to 17.34) different between groups, and survival analysis did not reveal any differences between groups (Figure 1).

**Association between nephrolithiasis and death**—One case cat died of renal causes after 43 months, and 1 control cat died of renal causes after 26 months. The proportion of cats that died of renal causes was not significantly (P = 0.957; OR, 1.08; 95% CI, 0.07 to 17.34) different between groups, and survival analysis did not reveal any differences between groups in regard to time to death from renal causes (Figure 2).

Overall, 6 case and 2 control cats died during the study. However, the proportion of cats that died of any cause was not significantly (P = 0.186; OR, 2.63; 95% CI, 0.62 to 12.09) different between groups, and survival analysis did not reveal any differences between groups in regard to time to death from any cause (Figure 3).

### Table 1—Mean ± SD values for clinical, serum biochemical, and urine evaluations performed in cats with naturally occurring stage 2 or 3 CKD that did (n = 7) or did not (n = 7) have nephroliths and were followed up for 24 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference range</th>
<th>Baseline (nephroliths)</th>
<th>No nephroliths (n = 7)</th>
<th>P-value</th>
<th>12 months (n = 7)</th>
<th>No nephroliths (n = 7)</th>
<th>P-value</th>
<th>24 months (n = 7)</th>
<th>No nephroliths (n = 7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS</td>
<td>NA</td>
<td>3.7 ± 1.0</td>
<td>3.1 ± 0.4</td>
<td>0.18</td>
<td>4.2 ± 0.8</td>
<td>3.1 ± 0.7</td>
<td>0.14</td>
<td>3.7 ± 0.8</td>
<td>3.7 ± 0.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>NA</td>
<td>5.0 ± 1.2</td>
<td>4.2 ± 0.9</td>
<td>0.12</td>
<td>5.3 ± 1.0</td>
<td>4.1 ± 0.6</td>
<td>0.06</td>
<td>5.2 ± 1.0</td>
<td>4.0 ± 0.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120–160</td>
<td>141 ± 15</td>
<td>150 ± 20</td>
<td>0.33</td>
<td>145 ± 17</td>
<td>143 ± 13</td>
<td>0.33</td>
<td>142 ± 14</td>
<td>150 ± 17</td>
<td>0.28</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>26–42</td>
<td>33.0 ± 5.2</td>
<td>34.1 ± 2.9</td>
<td>0.63</td>
<td>34.2 ± 5.2</td>
<td>32.6 ± 3.6</td>
<td>0.61</td>
<td>34.9 ± 5.4</td>
<td>32.3 ± 5.0</td>
<td>0.53</td>
</tr>
<tr>
<td>SUN (mg/dL)</td>
<td>14–33</td>
<td>46.9 ± 9.6</td>
<td>38.6 ± 8.7</td>
<td>0.12</td>
<td>47.7 ± 14.8</td>
<td>41.3 ± 6.0</td>
<td>0.16</td>
<td>47.5 ± 17.6</td>
<td>51.1 ± 17.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.6–1.4</td>
<td>2.8 ± 0.7</td>
<td>2.6 ± 0.4</td>
<td>0.48</td>
<td>2.9 ± 0.8</td>
<td>2.7 ± 0.5</td>
<td>0.34</td>
<td>2.9 ± 1.0</td>
<td>3.5 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>17–26</td>
<td>18.6 ± 3.3</td>
<td>19.4 ± 2.2</td>
<td>0.58</td>
<td>18.7 ± 2.6</td>
<td>19.0 ± 2.1</td>
<td>0.66</td>
<td>17.2 ± 1.7</td>
<td>18.0 ± 1.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.9–11.3</td>
<td>10.3 ± 0.2</td>
<td>9.9 ± 0.4</td>
<td>0.06</td>
<td>10.7 ± 0.6</td>
<td>9.9 ± 0.3</td>
<td>0.03</td>
<td>10.5 ± 0.7</td>
<td>10.1 ± 0.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Urated calcium (mg/dL)</td>
<td>1.25–1.45</td>
<td>1.39 ± 0.05</td>
<td>1.37 ± 0.05</td>
<td>0.48</td>
<td>1.45 ± 0.10</td>
<td>1.36 ± 0.16</td>
<td>0.12</td>
<td>1.38 ± 0.07</td>
<td>1.39 ± 0.11</td>
<td>0.27</td>
</tr>
<tr>
<td>Phosphorous (mg/dL)</td>
<td>3.8–8.2</td>
<td>4.1 ± 0.7</td>
<td>3.5 ± 0.7</td>
<td>0.16</td>
<td>4.2 ± 0.9</td>
<td>3.7 ± 0.6</td>
<td>0.15</td>
<td>4.7 ± 1.3</td>
<td>4.3 ± 1.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Parathormone (pmol/L)</td>
<td>0–4</td>
<td>4.60 ± 2.3</td>
<td>4.1 ± 2.8</td>
<td>0.73</td>
<td>4.7 ± 5.0</td>
<td>3.6 ± 2.7</td>
<td>0.19</td>
<td>7.4 ± 5.4</td>
<td>3.8 ± 2.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.9–5.3</td>
<td>4.40 ± 0.41</td>
<td>4.31 ± 0.45</td>
<td>0.47</td>
<td>4.35 ± 0.49</td>
<td>4.26 ± 0.21</td>
<td>0.94</td>
<td>4.32 ± 0.31</td>
<td>4.30 ± 0.42</td>
<td>0.70</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>147–158</td>
<td>151.7 ± 1.7</td>
<td>151.6 ± 2.4</td>
<td>0.90</td>
<td>153.0 ± 1.7</td>
<td>151.6 ± 1.5</td>
<td>0.58</td>
<td>152.5 ± 1.8</td>
<td>152.4 ± 1.7</td>
<td>0.91</td>
</tr>
<tr>
<td>USG</td>
<td>NA</td>
<td>0.024 ± 0.001</td>
<td>0.016 ± 0.005</td>
<td>0.11</td>
<td>0.025 ± 0.010</td>
<td>0.015 ± 0.002</td>
<td>0.13</td>
<td>0.023 ± 0.010</td>
<td>0.014 ± 0.002</td>
<td>0.12</td>
</tr>
<tr>
<td>UPUC ratio</td>
<td>&lt; 0.5</td>
<td>0.17 ± 0.12</td>
<td>0.06 ± 0.07</td>
<td>0.05</td>
<td>0.18 ± 0.04</td>
<td>0.10 ± 0.19</td>
<td>0.09</td>
<td>0.40 ± 0.30</td>
<td>0.17 ± 0.18</td>
<td>0.09</td>
</tr>
</tbody>
</table>

BSC = Body condition score. NA = Not applicable. USG = Urine specific gravity. UPUC = Urine protein-to-urate creatinine.
Association between nephrolithiasis and progression of CKD—The slope of the regression line for the reciprocal of serum creatinine concentration over time among cats with nephroliths (slope, 0.00003) was not significantly different from the slope of the regression line for cats without nephroliths (0.0022; Figure 4).

Biologic behavior of nephroliths—Six of the 7 case cats had bilateral nephroliths at the time of study enrollment, and 1 had unilateral nephroliths. Follow-up radiographs were not obtained in the case cat that was euthanized after 10 months because of lymphosarcoma, but were obtained after 24 months in the remaining 6 case cats. In 3 cats, additional follow-up radiographs were obtained after 33 to 72 months.

In 5 of the 6 case cats for which follow-up radiographs were available, no change in the radiographic size or number of nephroliths was identified. In the remaining cat, the size and number of nephroliths were increased at 58 months. At 72 months, multiple radiodense cystoliths were detected; however, the nephroliths had not changed any further in size or number. The cat was euthanized at this time because of clinical signs associated with intestinal leiomyosarcoma, and at necropsy, 2 irregular nephroliths were observed in the right renal pelvis. Quantitative urolith analysis revealed that the nephroliths were composed of 100% calcium oxalate monohydrate. The cystoliths were also composed of 100% calcium oxalate monohydrate. Unfortunately, nephroliths in the left renal pelvis were not collected at necropsy.

One cat with bilateral nephroliths was euthanized at 39 months because of progressive dyspnea secondary to laryngeal paralysis. At necropsy, both kidneys were small and irregular. Histologic examination of kidney specimens revealed severe, diffuse, cortical atrophy with diffuse interstitial fibrosis, glomerular sclerosis, and multifocal lymphocytic aggregates. A single urolith (1 × 2 mm) was observed in the right renal pelvis, and 2 uroliths (2 × 2 mm and 3 mm) were observed in the left renal pelvis. Quantitative analysis revealed that all 3 uroliths were composed of 100% calcium oxalate monohydrate with surface crystals of 100% calcium phosphate.

A necropsy was performed on the cat that was euthanized at 10 months because of lymphosarcoma. Although nephroliths were found in both renal pelvices, they were not submitted for quantitative analysis. Another case cat was euthanized at 26 months because of colonic carcinoma. At necropsy, granular material was observed in both renal pelvices, but it was not submitted for analysis. The case cat that was euthanized at 43 months because of uremic crisis did not undergo necropsy, and the remaining case cat was still alive at the end of the study.

None of the 7 control cats developed radiographic evidence of nephroliths during the time of the study. A necropsy was performed on 1 of the 2 control cats that died. This cat died at 30 months as a result of intra-abdominal bleeding secondary to rupture of a hepatic or pancreatic adenocarcinoma. Both kidneys were small, but there was no macroscopic evidence of uroliths in the kidneys, ureters, bladder, or urethra. Histologic examination of the kidneys revealed marked lymphoplasmacytic nephritis with marked fibrosis.

Discussion

Results of the present study support the hypothesis that nephrolithiasis in cats with stage 2 or 3 CKD is not associated with increases in mortality rate or disease progression. In particular, we did not find any association between nephrolithiasis and incidence of uremic crisis or death. Also, we did not find any clinically important differences in results of clinical or laboratory evaluations between cats with nephroliths and cats without. Taken together, these findings suggest that nephrolithiasis does not alter the progression of kidney disease in cats and support the recommendation that nephroliths in cats with CKD be treated medically.

The fact that most nephroliths in cats are composed of calcium salts and are not amenable to dissolution may seem to suggest that surgical removal is warranted. Given...
the potential complications associated with nephrotomy for surgical removal of nephroliths, the risks and benefits of this procedure should be carefully weighed.13 Importantly, a recent study6 examining unilateral nephropathy in cats with normal renal function revealed a modest reduction in renal function in the surgically treated kidney, compared with the contralateral control kidney. It is probable that in cats with CKD, nephrotomy would result in an even greater reduction in renal function and, in some instances, could precipitate a uremic crisis. Thus, the risk that surgical removal of nephroliths could result in further deterioration of renal function in cats with CKD must be compared with the potential risks of allowing nephroliths to remain in place.

To our knowledge, there are no published reports demonstrating that sterile nephroliths contribute to a progressive decline in renal function. In a previous study9 of 88 cats with CKD that underwent abdominal radiography, 41 (47%) had upper urinary tract uroliths. Of these 41 cats, however, only 4 (10%) had ureteroliths, suggesting either that most nephroliths remain in the kidneys or that most ureteroliths pass into the bladder. Importantly, migration of nephroliths into the ureters often results in some degree of obstruction and subsequent loss of renal function. Acute ureteral obstruction is increasingly recognized as an important syndrome in cats that may have catastrophic consequences, particularly in patients with preexisting CKD.24 In our clinical experience, few obstructive ureteroliths will migrate into the bladder, leaving surgical intervention as the only option for treatment. However, ureteral surgery is technically demanding and associated with high morbidity and mortality rates. A recent retrospective study15 of 153 cats with ureteral calculi revealed a postoperative complication rate of 31% and a perioperative mortality rate of 18%. Acute ureteral obstruction secondary to migration of nephroliths into the ureters was not documented in any of the cats in the present study. However, 1 case cat was euthanized at 43 months after developing an acute uremic crisis. Because abdominal radiography was not performed prior to euthanasia and a necropsy was not obtained, acute ureteral obstruction secondary to nephrolith migration could not be ruled out as the underlying cause of the uremic crisis. Nevertheless, even if acute ureteral obstruction was the precipitating cause of the uremic crisis in this cat, the incidences of uremic crises and death from renal causes did not differ significantly between cats with nephroliths and cats without.

Hypercalcemia has been previously identified in some cats with calcium oxalate urolithiasis.15 A report15 of epidemiologic data from the Minnesota Urolith Center, for instance, revealed mild hypercalcemia (serum calcium concentration between 11.1 and 13.5 mg/dL) in 35% of cats with calcium oxalate uroliths. A retrospective study16 of 71 hypercalcemic cats found that 11 (15%) had uroliths and that all of the uroliths retrieved from the 8 cats that underwent surgery were composed of calcium oxalate. Similar results were observed in the present study, with hypercalcemia documented in 2 of the 7 cats with nephroliths.

Although mean serum calcium concentration was not significantly different between case and control cats in the present study, the only 2 cats documented to have hypercalcemia also had nephroliths. One of the 2 hypercalcemic cats had persistently high serum total and ionized calcium concentrations, while serum parathormone concentration remained within reference limits. Because this cat was still alive at the time of the present study, the mineral composition of its nephroliths was not known. The underlying cause for the hypercalcemia in this cat was not determined, but renal secondary hyperparathyroidism was considered unlikely because of the normal parathormone concentrations and high serum ionized calcium concentrations. Plausible explanations for the hypercalcemia in this cat include consumption of a vitamin D–enhanced diet or idiopathic hypercalcemia.17 The other hypercalcemic cat had high serum total calcium and parathormone concentrations while serum ionized calcium concentrations were within reference limits. This cat consumed an adult maintenance diet throughout the study and was euthanized at 39 months because of progressive laryngeal paralysis. Biochemical data from this cat suggested that renal secondary hyperparathyroidism was the most likely cause of hypercalcemia. Uroliths collected from both kidneys at necropsy were composed of 100% calcium oxalate monohydrate.

In 6 of the 7 case cats in the present study, abdominal radiography was performed at the time of study enrollment and again 24 months later, and in 3 cats, additional abdominal radiographs were obtained after this time. An increase in the size or number of nephroliths was observed in only 1 cat and was not seen until 58 months after study enrollment. None of the control cats developed radiographic evidence of nephrolithiasis during the study. It is probable that the size and number of nephroliths remained stable in all but one of the cats with nephroliths because the conditions required for the initial formation of nephroliths were no longer present. Growth of existing uroliths is influenced by many factors, including diet, urine solute concentration, urine volume, and urine concentration of urolith inhibitors (eg, pyrophosphate, citrate, and glycoproteins).18,19 In case cats, it is possible that formation of nephroliths preceded the development of CKD. Once CKD developed, the increased formation of urine would have been associated with reductions in the urine concentrations of calculogenic substances, which would minimize calculus growth and formation of additional uroliths.

Another possible explanation for the stability in size and number of the nephroliths observed in case cats could be related to the composition of the renal diet. Most renal diets are formulated to minimize several risk factors for formation of calcium-containing uroliths. Dietary risk factors thought to be associated with calcium oxalate urolith formation in humans include consuming a urine-acidifying diet and consuming diets high in protein, phosphorous, oxalate, and sodium.20 and most commercially available renal diets are formulated to promote an alkaline urine pH and contain reduced quantities of protein, phosphorous, and sodium.21 However, appropriately designed and implemented clinical trials will be required to prove this hypothesis. In addition, only 3 of the 7 case cats in the present study were fed the renal diet. The cats with radiographic evidence of an increase in nephrolith size and number were fed the maintenance diet.

There were a number of limitations to the present study, including the small number of cats available for study. Importantly, the limitations of a single determination of serum creatinine concentration as an index of renal function have been documented.22 In dogs, however, serial measurements of serum creatinine concentration have been shown to be of value in establishing trends in glomerular filtration.
Retrospective case-control studies are inherently susceptible to both sampling and observational bias. In the present study, the case and control cats were selected from a group of cats that were concurrently participating in a prospective clinical trial evaluating the effects of dietary modification on the progression of stage 2 and 3 CKD. Because only cats with stable renal function were included in that study, the present study may have excluded cats with nephroliths in which there was an association between CKD and nephrolithiasis. It is also possible that other inclusion criteria for the previous study inadvertently selected for confounding factors that may have influenced the outcomes for case and control cats in the present study. In the present study, case and control cats were matched to control for the 2 most obvious confounders, diet and age, but other factors may have also played a role.

In conclusion, results of this retrospective case-control study support the hypothesis that the presence of nephroliths at the time of initial diagnosis in cats with naturally occurring stage 2 or 3 CKD is not associated with a significant increase in mortality rate or disease progression. Validation of this hypothesis, however, would require a randomized controlled trial evaluating medical versus surgical management of nephrolithiasis in cats with CKD. Likewise, appropriately controlled clinical studies are needed to evaluate the association between nephrolithiasis and CKD. Pending results of such studies, we advocate medical management of nephroliths in cats with CKD.


Appendix

Criteria for therapeutic stages of CKD in cats.23

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (no azotemia)</td>
<td>Markers of kidney disease* are present. Serum creatinine &lt; 1.6 mg/dL. Proteinuria subclassification: P, NP, or BP. Hypertension subclassification: Hc, Hnc, NH, BH, or HND.</td>
</tr>
<tr>
<td>2 (mild azotemia)</td>
<td>Markers of kidney disease are present. Serum creatinine 1.6 to 2.8 mg/dL. Proteinuria subclassification: P, NP, or BP. Hypertension subclassification: Hc, Hnc, NH, BH, or HND.</td>
</tr>
<tr>
<td>3 (moderate azotemia)</td>
<td>Markers of kidney disease are present. Serum creatinine 2.9 to 5.0 mg/dL. Proteinuria subclassification: P, NP, or BP. Hypertension subclassification: Hc, Hnc, NH, BH, or HND.</td>
</tr>
<tr>
<td>4 (severe azotemia)</td>
<td>Markers of kidney disease are present. Serum creatinine &gt; 5.0 mg/dL. Proteinuria subclassification: P, NP, or BP. Hypertension subclassification: Hc, Hnc, NH, BH, or HND.</td>
</tr>
</tbody>
</table>

*Markers of kidney disease include laboratory and diagnostic imaging abnormalities confirmed to be of renal origin.

P = Proteinuria; NP = No proteinuria; BP = Borderline proteinuria.

Hc = Hypertension with complications; Hnc = Hypertension with no complications; NH = No hypertension; BH = Borderline hypertension; HND = Hypertension not determined.