Effect of aluminum hydroxide on serum phosphate and fibroblast growth factor 23 concentrations in young adult cats with surgically induced chronic kidney disease

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OBJECTIVE
To describe serum fibroblast growth factor 23 (FGF-23) concentrations in young adult cats with remnant kidney model–induced chronic kidney disease (CKD) and to evaluate the effects of orally administered aluminum hydroxide (ALOH) on serum phosphate and FGF-23 concentrations in these cats.

ANIMALS
17 adult, purpose-bred cats with induced CKD and 13 healthy, age-matched cats.

METHODS
A prospective, randomized study. Cats with induced CKD fed a wet renal diet received treatment with ALOH (90 mg/kg/d, PO) on days 0 to 42 and no treatment on days 43 to 84 (treatment group, n = 9) or no treatment on days 0 to 84 (control group, n = 8). Standard serum and urine biochemical analyses and several parameters reflective of calcium-phosphate balance, including serum parathyroid hormone and FGF-23 concentrations, were evaluated at baseline and various time points, including days 42 and 84. Age-matched, healthy, community-owned cats underwent similar evaluations at a single time point. Baseline data from CKD cats were compared to those of healthy cats. Longitudinal data from CKD cats were compared over time.

RESULTS
Serum phosphate, total and ionized calcium, and FGF-23 concentrations were significantly higher in CKD cats at baseline relative to healthy cats (all \( P \leq .009 \)). Serum phosphate concentration did not change significantly over time in either CKD group; however, FGF-23 concentrations significantly increased over time in the control group (\( P < .02 \)) but not the treatment group (\( P = .059 \)).

CLINICAL RELEVANCE
Aluminum hydroxide did not reduce serum phosphate or FGF-23 concentrations in this small study of cats with induced CKD chronically eating a phosphate-restricted diet.

Keywords: calcium, parathyroid hormone, vitamin D, calcitriol, phosphate binder

Chronic kidney disease (CKD) is common in the geriatric feline population, and phosphate retention due to reduced glomerular filtration rate is 1 of the most important factors implicated in the development of renal fibrosis, progression of CKD, and mortality of affected cats.1,2

Fibroblast growth factor 23 (FGF-23) is a small glycoprotein (approx 32 kDa), produced mostly by osteocytes and osteoblasts,3 that participates in the regulation of phosphate and calcium concentrations in the body.4 Fibroblast growth factor 23 receptors are expressed mainly in the kidney, bone and parathyroid gland, and their activation requires binding of FGF-23 and its coreceptor α-Klotho.4 Important functions of FGF-23 in the kidney are to reduce 1,25-dihydroxyvitamin D3 concentrations5 by decreasing its generation through inhibition of 1α-hydroxylase and increasing its inactivation through
stimulation of 24-hydroxylase and to increase the urinary excretion of phosphate by inhibiting the sodium-phosphate cotransporters (NPT2a and NPT2c) in the proximal tubules. Additionally, FGF-23 reduces the production and secretion of parathyroid hormone (PTH). The production of FGF-23 is stimulated by dietary phosphate loading and high circulating concentrations of phosphate, 1,25-dihydroxyvitamin D, calcium, and PTH.

Human patients with CKD experience elevated serum FGF-23 concentrations before the development of hyperphosphatemia or hyperparathyroidism. The initial increase in FGF-23 concentrations helps maintain normophosphatemia in the early stages of CKD. Also, certain complications of CKD, such as anemia, cardiovascular disease, and infection, are associated with higher circulating concentrations of FGF-23 in human beings and mice. Several studies show a similar pattern in cats with CKD, for which serum FGF-23 concentrations are positively associated with advancing stages of CKD and serum phosphate concentrations, and identify FGF-23 as an early biomarker for the identification of phosphate derangements in CKD and prediction of worse outcomes in cats with nonazotemic and azotemic CKD.

Dietary phosphate intake influences serum concentrations of FGF-23 in human beings, mice, and cats, with high dietary phosphate intake increasing serum FGF-23 concentrations and low phosphate intake decreasing these concentrations. Adult, healthy cats had serum FGF-23 concentrations 5 or 3 times higher than baseline when given a diet with high organic or inorganic phosphate, respectively. The dietary management of phosphate retention in CKD through phosphate restriction is crucial for the survival and life quality of affected cats.

In advanced stages of CKD, commercial phosphate-restricted therapeutic feline renal diets often fail to maintain phosphate concentrations within the target range. In the present study using a remnant kidney model of CKD, dietary phosphate intake influences serum concentrations of FGF-23 in human beings, mice, and cats, with high dietary phosphate intake increasing serum FGF-23 concentrations and low phosphate intake decreasing these concentrations. Adult, healthy cats had serum FGF-23 concentrations 5 or 3 times higher than baseline when given a diet with high organic or inorganic phosphate, respectively. The dietary management of phosphate retention in CKD through phosphate restriction is crucial for the survival and life quality of affected cats.

The objectives of the study were (1) to describe serum FGF-23 concentrations in adult cats with a remnant kidney model of CKD and (2) to evaluate the effects of ALOH on the phosphate balance, particularly serum FGF-23 concentrations, in the same group of cats with induced renal insufficiency. We hypothesized that (1) median FGF-23 concentrations would be higher in adult cats with a remnant kidney model of CKD compared to healthy, age-matched control cats and that (2) serum concentrations of phosphate and FGF-23 in cats with a remnant kidney model of CKD would decrease after 6 weeks of ALOH administration when compared to pretreatment baseline and would rise again after 6 weeks of discontinuing the treatment.

Methods

Experimental design

This was a prospective, randomized, controlled, nonmasked clinical study. Cats with induced CKD underwent baseline health and calcium-phosphate balance evaluation (days −14 to −1) and were randomized to the ALOH treatment or the control group. The treatment group received treatment with ALOH powder (Phos-Bind; Rx Vitamins) at a dosage of 90 mg/kg/d, PO, divided into 45 mg/kg given twice daily mixed with wet food (days 0 to 42), followed by no ALOH treatment for another 6 weeks (washout period; days 43 to 84). The control group did not receive ALOH treatment for 12 weeks (days 0 to 84). Health and phosphate balance evaluations were performed throughout the study as outlined below. Baseline health and calcium-phosphate data from the CKD group were compared to those of prospectively recruited age-matched, healthy cats.

All procedures were approved by the University of Georgia (UGA) IACUC (Animal Use Protocol A2018-10-001-Y1-A1) and Clinical Research Committee (CR-665) and followed the American Association for Laboratory Animal Science guidelines for the humane care and use of laboratory animals.

Animals

All purpose-bred cats from a remnant kidney colony (n = 17; 9 spayed females and 8 neutered males) were enrolled in the CKD group. This group had an average age of 2 years 9 months (± 3 months) at baseline. The cats were obtained from a commercial source (Marshall Bioresources) and underwent a 2-stage 11/12 reduction in renal mass approximately 18 to 22 months prior to the start of the present study using a remnant kidney model of CKD previously described.

Apparently healthy, spayed female or neutered male cats, aged 2 to 4 years old and owned by community members of the College of Veterinary Medicine of the UGA, were prospectively recruited for the healthy cat group. A convenience sample of 10 to 16 cats was targeted. Cats were excluded if they had received corticosteroid treatment in the last 30 days, were receiving medications known to affect calcium or phosphate concentrations, or had been previously diagnosed with any chronic diseases. Cats were also excluded if their health evaluation (detailed below) revealed hyperphosphatemia (serum phosphate > 5.7 mg/dL; reference interval [RI], 2.8 to 5.7 mg/dL) or azotemia (serum creatinine [sCr] > 1.8 mg/dL; RI, 0.7 to 1.8 mg/dL).

Health and calcium-phosphate balance evaluation

Cats in the CKD group underwent a baseline evaluation (days −14 to −1), consisting of a physical examination (including body weight and body condition score [BCS]), indirect systolic blood pressure (SBP) determination using Doppler sphygmomanometry, CBC, serum biochemistry profile (which included sCr, serum urea nitrogen [SUN],
phosphate, and total calcium [tCa] concentrations), serum symmetric dimethylarginine (SDMA), FGF-23, 1,25-dihydroxyvitamin D, PTH, ionized calcium (iCa), and 25-hydroxyvitamin D concentrations, urinalysis, urinary protein-to-creatinine ratio (UP:Cr), urinary phosphate-to-creatinine ratio (UPhos:Cr), and urine culture. Physical examination, serum phosphate, iCa, PTH, 25-hydroxyvitamin D, and UPhos:Cr were reevaluated on days 14 ± 2, 28 ± 2, 42 ± 5, 70 ± 2, and 84 ± 5. Additionally, CBC, serum biochemistry profile, serum SDMA, FGF-23, and 1,25-dihydroxyvitamin D concentrations, urinalysis, and UP:Cr were reevaluated on days 42 ± 2 and 84 ± 5.

Cats screened for enrollment in the healthy group underwent a physical examination, indirect SBP, CBC, serum biochemistry profile, serum SDMA, iCa, PTH, 25-hydroxyvitamin D, and FGF-23 concentrations, urinalysis, and UP:Cr at a single time point. Due to an oversight in study design, serum 1,25-dihydroxyvitamin D concentrations and UPhos:Cr were not evaluated in healthy cats.

In all instances, physical examinations were performed by a veterinarian, and indirect SBP was determined by a veterinary technician or veterinarian using Doppler sphygmomanometry and following the guidelines set forth by the American College of Veterinary Internal Medicine.28

Randomization

To facilitate daily study activities, cats in the CKD group were enrolled in 2 cohorts (cohort 1, all females; cohort 2, all males) that entered the study 29 days apart. For each cohort, cats were sorted based on baseline serum phosphate concentrations, from highest to lowest, and grouped in pairs. For each pair, cats were randomly assigned to the control or treatment group by drawing tickets out of an envelope. For cohort 2, for which there was an odd number of cats, the last cat was allocated to the treatment group.

Feeding and concomitant medications

Prior to study enrollment, cats in the CKD group were being fed Hill’s Prescription Diet k/d with Chicken Dry Cat Food (Hill’s Pet Nutrition, Inc; 116 mg/100 kcal phosphorus; calcium-to-phosphorus [Ca:P] ratio, 1.40; n = 16) or Royal Canin Veterinary Diet Multifunction Renal Support + Hydrolyzed Protein Dry Cat Food (ROYAL CANIN® Veterinary Diet Multifunction Renal Support + Hydrolyzed Protein Dry Cat Food, Hill’s Pet Nutrition, Inc; 124 mg/100 kcal phosphorus; Ca:P ratio, 1.45; n = 1) dry kibble. At least 19 weeks before the start of the study, all cats were transitioned to a similar clinical renal diet in canned form (Hill’s Prescription Diet k/d Pâté with Chicken Cat Food, Hill’s Pet Nutrition, Inc; 124 mg/100 kcal phosphorus; Ca:P ratio, 1.73) to allow for mixing of the Aloh with the food. A different canned food (Hill’s Prescription Diet k/d Kidney Care Chicken & Vegetable Stew Wet Cat Food, Hill’s Pet Nutrition, Inc; 111 mg/100 kcal phosphorus; Ca:P ratio, 1.58) was offered to cats to encourage eating during the study period if needed. Cats were fed twice daily, in the morning from 8 AM to 9 AM and in the evening from 4 PM to 5 PM, and daily food consumption was monitored beginning at baseline (days −14 to −1) and throughout the duration of the study. Food consumption was registered for each feeding by weighing the food offered and remaining in the cats’ respective bowls at each meal, and percentages of daily food consumption were calculated. Municipal tap water was provided ad libitum.

Concomitant medications commonly used for the treatment of CKD and its comorbidities, including amlodipine for the treatment of systemic arterial hypertension, and mirtazapine, maropitant, SC fluids, and potassium and probiotic supplementation as supportive therapies were allowed.

Husbandry of purpose-bred cats

Cats were accommodated in an indoor laboratory-housing environment managed by the University Animal Resources of the UGA. The housing ensured a controlled environment with 12 to 15 air changes/h, a 12-hour light/dark cycle, and room temperatures of 22.2 ± 2°C. The cats were single housed in USDA-approved cages with food and water bowls, an elevated shelf or hammock, a litter box, and toys for environmental enrichment. The litter boxes contained regular disposable litter material or nonabsorbable disposable litter (NOSORB; Catco Inc) on the days that urine samples were collected.

Sample collection

For the CKD group, at each time point, cats were fasted for at least 6 hours prior to sampling and were sedated to minimize stress associated with venipuncture. Sedation included alfaxalone (1 to 2 mg/kg, IM), butorphanol (0.2 to 0.3 mg/kg, IM), and midazolam (0.2 to 0.4 mg/kg, IM). For the healthy group, cats were fasted for at least 6 hours prior to sampling, and sedation with butorphanol (0.3 to 0.5 mg/kg, IM) was used if deemed necessary for each individual cat. Blood was collected from the jugular, saphenous, or cephalic vein and placed into red-top serum tubes and EDTA tubes previously labeled. Blood placed into 1-mL-EDTA tubes was gently mixed, and red-top tubes were allowed to clot for at least 30 minutes. Serum red tubes were placed in a centrifuge and spun at 3,000 × g for 10 minutes. Serum was separated and placed in prelabeled vials within 60 minutes of collection and stored at −20 to −80°C until shipping. Urine samples were collected via cystocentesis or with a syringe from litter pans lined with nonabsorbent cat litter (NOSORB; Catco Inc) and transferred to a labeled glass tube containing no additive.

Clinicopathologic analyses

Blood and urine samples were submitted to the Clinical Pathology Laboratory, College of Veterinary Medicine at the UGA for CBC, serum biochemistry, urinalysis, and urine creatinine, protein, and phosphate concentrations for determination of UP:Cr and UPhos:Cr. Urine protein was measured using a turbidimetric method (benzethonium chloride). Urine creatinine concentration was measured using an enzymatic method in undiluted samples. Samples were automatically diluted 1:4 if the concentration exceeded the reportable limit (ie, 98 mg/dL).
Measurements of serum SDMA and FGF-23 concentrations were performed by commercial laboratories (IDEXX Reference Laboratories and IDEXX BioAnalytics, respectively). The measurement of intact FGF-23 concentrations used a sandwich ELISA (Kainos Laboratories) that was validated in feline serum by evaluating precision, accuracy, potential sample interferences, and sample stability. Samples were diluted 1:5. The results of 299 pg/mL or less or 4,000 or higher are not reported as discrete numerical values by the laboratory.

Measurements of serum PTH, iCa, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D concentrations were performed by the Veterinary Diagnostic Laboratory of Michigan State University. Serum PTH concentrations were measured using an automated intact PTH chemiluminescent immunometric assay (IDS-STAT PTH; Immunodiagnostic Systems Ltd). Serum iCa concentrations were measured using an iCa-selective electrode (Stat Profile PRIME ES Comp Plus Analyzer; Nova Biomedical). Serum 25-hydroxyvitamin D and 1,25 hydroxyvitamin D concentrations were measured using radio-immunoassays (25-Hydroxyl Vitamin D RIA and 1,25-Dihydroxy Vitamin D RIA; Immunodiagnostic Systems Ltd, respectively).

All samples analyzed at external laboratories were shipped overnight in an appropriate container that kept them in optimal conditions.

**Statistical analyses**

Baseline clinicopathologic continuous data were assessed for normality using the Shapiro-Wilks and the D’Agostino and Pearson tests and visual assessment of quantile-quantile plots. Normally distributed data were presented as median (range) and compared between these groups using the 2-tailed Welch t test. Non-normally distributed data were presented as mean ± SD and compared between the 2 main groups (ie, CKD group vs healthy cat group) using the 2-tailed Welch t test. Non-parametric testing (ie, the Mann-Whitney test) was used to compare these data between groups.

Longitudinal clinicopathological data from the CKD cats in the treatment and control groups were compared between time points using the Friedman test with pairwise comparisons using Dunn multiple comparison testing. The absolute change in serum phosphate and FGF-23 concentrations at each of days 42 and 84, relative to day 0, was calculated and compared between the treatment and control group using the 2-tailed Mann-Whitney test. Food consumption was compared between treatment groups over time using the 2-way ANOVA.

Statistical analyses were performed with commercially available statistical software (Graph Pad Prism, version 9.5.1, GraphPad Software Inc), and P < .05 was considered significant for all comparisons.

**Results**

**Demographic and renal function data of CKD and healthy cats**

Sixteen apparently healthy cats were screened for inclusion in the healthy cat group, of which 13 cats met the enrollment criteria. Two cats were excluded due to hyperphosphatemia and 1 cat was excluded due to azotemia. Of the 13 cats included in the healthy group, 7 were females and 6 were males. The breeds represented were domestic shorthair (n = 9), Siamese (n = 2), domestic long hair (n = 1), and Sphynx (n = 1).

Consistent with their health and disease status, cats in the CKD group had significantly higher sCr (P < .001), SDMA (P < .0001), and SUN (P < .05) concentrations, UP:Cr (P = .0012), and SBP (P = .0042) compared to the healthy cat group (Table 1). Cats in the CKD group had significantly lower body weight (P < .0001) and urine specific gravity (USG; P < .001) than those in the healthy cat group. For cats in the CKD group, USG was > 1.035 in 2 of 17 (11.8%) and < 1.035 in 15 of 17 (88.2%) cats. Conversely, 12 of 13 (92.3%) healthy cats had USG > 1.035 and 1 of 13 (7.7%) had USG < 1.035. Urine cultures performed at baseline were negative for the CKD cats.

According to the IRIS CKD staging (http://www.iris-kidney.com/guidelines/staging.html), 1 of 17 cats in the CKD group was in stage 1, 12 of 17 cats were in stage 2, and 4 of 17 cats were in stage 3. Regarding

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### Table 1—Clinicopathological variables in cats with surgically induced chronic kidney disease (CKD) at baseline and age-matched apparently healthy control cats.

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n = 13)</th>
<th>CKD (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>4.91 ± 0.87</td>
<td>3.96 ± 0.73</td>
<td>.0042</td>
</tr>
<tr>
<td>BCS (1)</td>
<td>7 (5–8)</td>
<td>6 (5–8)</td>
<td>.2017</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>119.7 ± 11.97</td>
<td>158.1 ± 26.26</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SCR (mg/dL; RI, 0.7–1.8 mg/dL)</td>
<td>1.5 (0.5–1.8)</td>
<td>2.3 (1.5–4.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SDMA (μg/dL; RI, 0–14 μg/dL)</td>
<td>11 (7–14)</td>
<td>26 (12–52)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SUN (mg/dL; RI, 18–35 mg/dL)</td>
<td>23 (17–29)</td>
<td>27 (18–71)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>USG (a)</td>
<td>1.051 (1.028–1.060)</td>
<td>1.019 (1.008–1.063)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>UP:Cr (b)</td>
<td>0.110 (0.08–0.31)</td>
<td>0.248 (0.101–0.472)</td>
<td>&lt;.0012</td>
</tr>
</tbody>
</table>

**Notes:**

(a) Mean ± SD, unpaired t test with a Welch correction. (b) Median (range), Mann-Whitney test.

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BCS = Body condition score. RI = Reference interval. SBP = Systolic blood pressure. SCR = Serum creatinine. SDMA = Symmetric dimethylarginine. SUN = Serum urea nitrogen. UP:Cr = Urine protein creatinine ratio. USG = Urinary specific gravity.

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proteinuria substaging, 7 of 17 were nonproteinuric, 9 of 17 were borderline proteinuric, and 1 of 17 was proteinuric. Regarding substaging according to SBP measurement, 5 of 17 were normotensive, 3 of 17 were prehypertensive, 5 of 17 were hypertensive, and 4 of 17 were severely hypertensive; however, situational hypertension was deemed likely for 4 cats that displayed outward signs of stress during SBP measurements despite ongoing acclimation to the procedure and had no signs of extrarenal target organ damage, including normal fundic examination.

Concomitant medications
Cats with CKD diagnosed with pathologic systemic arterial hypertension (5/17; n = 3 in the treatment group and n = 2 in the control group) were receiving treatment with amlodipine (0.625 to 2.5 mg/cat, PO, q 24 h) with their morning meal during the study. Three cats in the treatment group were receiving SC fluids (Lactated Ringer’s solution, 100 to 175 mL, q 24 h or 48 h) with potassium chloride (10 to 30 mEq/L) for hydration and electrolyte support. Mirtazapine (Mirataz; 2 mg/cat, transdermal, q 24 h to q 48 h) was used in 5 cats (1 control and 4 treatment) to stimulate appetite. Additionally, 7 cats (n = 2 in the treatment group and n = 5 in the control group) were receiving potassium gluconate (half to 1 and a half tablets, 2 mEq, PO, twice a day) for the treatment of hypokalemia, which developed subsequently to the diet change. One cat in the treatment group was administered darbepoetin (1 µg/kg, SC, weekly to every other week) and iron (50 mg/cat, IM, monthly). One cat in the treatment group was administered maropitant (1 mg/kg, PO, q 24 h) for 7 days, and another cat in the treatment group was prescribed a probiotic supplement (Fortiflora, Purina; 1 packet per day) for 7 days.

Calcium-phosphate balance data in CKD and healthy cats
The median serum FGF-23 (P < .0001) and phosphate (P = .0005) concentrations and calcium-phosphate (Ca x P) product (P = .0003) were significantly higher in the CKD group at pretreatment baseline relative to the healthy cat group. The mean tCa (P = .0042) and iCa (P = .0088) concentrations were also significantly higher in the CKD group at baseline compared to the healthy controls (Figure 1). There was no significant difference in serum PTH and 25-hydroxyvitamin D concentrations between groups.

Renal function and calcium-phosphate balance data in CKD cats by treatment group
The baseline clinicopathologic characteristics of each CKD group (ie, treatment or untreated control group) are presented in Table 2. All cats were believed to have stable CKD at enrollment. However, 1 cat in the treatment group experienced acute on CKD of unknown etiology that improved during the course of the study. Despite this, overall, there were no statistically significant differences in renal function parameters (sCr, SDMA, SUN, USG, UP:Cr, and hematocrit) over time for either of the CKD groups (treatment or control; Supplementary Figure S1).

There was no statistically significant difference in median serum phosphate concentration across different time points for either the treatment or control group (P = .69 and P = .10, respectively; Figure 2; Supplementary Material S1). This remained true after the exclusion of the 1 cat that experienced acute on CKD during the study period (P = .57). At baseline, 12 of 17 of the CKD cats had serum phosphate concentrations above the recommended target set forth by IRIS (≥ 4.6 mg/dL); of these, 6 cats were in the treatment group (range, 4.7 to 14.0 mg/dL) and 6 in the control group (range, 4.6 to 5.4 mg/dL). After 6 weeks of ALOH, 6 of 9 cats in the treatment group (range, 4.8 to 18.4 mg/dL) and 4 of 8 cats in the control group (range, 5.0 to 5.4 mg/dL) still had serum
phosphate concentrations above this target. These include 3 of 6 treatment group cats that had serum phosphate ≥ 4.6 mg/dL at baseline and 3 additional cats that experienced an increase in serum phosphate while receiving ALOH. On day 84, after a washout period of 6 weeks for the treatment group, serum phosphate concentrations were above the IRIS target in 7 of 9 cats in the treatment group (range, 5 to 9.9 mg/dL) and 6 of 9 in the control group (range, 4.6 to 5.9 mg/dL). Eight cats had serum phosphate ≥ 4.6 mg/dL throughout all time points, 4 in the treatment group and 4 in the control. The median absolute changes in serum phosphate and FGF-23 concentrations at days 42 or 84, relative to baseline, were not different between the treatment groups (Figure 3).

Baseline serum FGF-23 concentrations were > 400 pg/mL in 12 CKD cats (n = 7 in the treatment group and n = 5 in the untreated control group). In the CKD untreated control group, median serum FGF-23 concentration increased over time (overall \(P < .02\), from 460.5 pg/mL at baseline to 768.0 pg/mL at day 42 to 979.5 pg/mL at day 84 (day 42 vs day 84 adjusted \(P = .037\); Figure 2). Although median serum FGF-23 concentrations were also numerically higher at days 42 (1,753 pg/mL) and 84 (1,829 pg/mL), relative to baseline (1,144 pg/mL) in the treatment group, this difference did not reach statistical significance (overall \(P = .059\)).

Total hypercalcemia (ie, \(tCa > 11.0 \text{ mg/dL}\)) was present at baseline in 8 CKD cats (n = 5 in the treatment group and n = 3 in the untreated control group). There was a significant, mild change in median \(tCa\) in the treatment group (baseline, 11.1 mg/dL; day 42, 11.3 mg/dL; day 84, 10.7 mg/dL; overall \(P < .025\); day 0 vs day 42 adjusted \(P = .04\); no other significant pairwise comparisons) but not the control group (\(P = .36\)) over time. Conversely, there was an overall significant, mild difference in median \(Ca \times P\) over the course of the study in the control group (baseline, 55.85 mg²/dL²; day 42, 53.45 mg²/dL²; day 84, 58.1 mg²/dL²; overall \(P = .047\); day 42 vs day 84 adjusted \(P = .037\); no other significant pairwise comparisons) but not in the treatment group (\(P = .97\)).

No statistical difference over time was found for serum PTH, 25-hydroxyvitamin D, and 1,25-hydroxyvitamin D concentrations and UPhos:Cr in either CKD group (Figure 2).

**Food consumption, body weight, and BCS in CKD cats during ALOH treatment**

Food consumption was variable from cat to cat (\(P < .0001\)) and increased over time in both groups (\(P < .001\), but there was no significant difference between groups. In the treatment group, 7 of 9 cats ate > 85% of their renal diet with the ALOH, and the remaining cats (2/9) ate 75% to 65% of their renal diet on average. In the control group, 6 of 8 cats ate > 83% of their renal diet, and 2 of 8 ate 70% to 80% of their renal diet on average. A food that was perceived as more palatable (Hill’s Prescription Diet k/d Kidney Care Chicken & Vegetable Stew Wet Cat Food, half of a can, twice a day) was offered to the 1 treatment group cat that experienced acute on CKD for 38 consecutive days during the study, starting at day 46 (ie, during the washout period).

A significant difference in median BCS over time was found in both groups, which decreased from 6 of
Figure 2—Median (IQR) serum phosphate (A), total calcium (B), ionized calcium (C), calcium-phosphorus product (D), 25-hydroxyvitamin D (E), 1,25-hydroxyvitamin D (F) parathyroid hormone (G), fibroblast growth factor 23 (H), and urinary phosphorus-to-creatinine ratio (I) in cats with surgically induced chronic kidney disease (n = 17), randomized to receive aluminum hydroxide (90 mg/kg/d, PO) for 42 days followed by no intestinal phosphate binder treatment for another 42 days (treatment group, n = 9) or no intestinal phosphate binder treatment for 84 days (control group, n = 8). The shaded areas represent the reference interval for each parameter. For fibroblast growth factor 23 (H), the light-gray shade represents "normal" and the darker gray shade represents "borderline" values as defined by the commercial laboratory. For phosphate (A), the dotted line represents the upper limit of the International Renal Interest Society target of 4.6 mg/dL. *Denotes an overall significant difference in that group over time as assessed by the Friedman test. The color of the symbol denotes the treatment group it refers to. Significant pairwise comparisons are denoted in parentheses. D = Day. NSPC = No significant pairwise comparisons.

Figure 3—Dot plot of absolute change in serum phosphate concentrations (∆Phos) at day 42 (A) and day 84 (C) and absolute change in serum fibroblast growth factor 23 (FGF-23) concentrations (∆FGF-23) at day 42 (B) and day 84 (D) in cats with surgically induced chronic kidney disease (n = 17), randomized to receive aluminum hydroxide (90 mg/kg/d, PO) for 42 days followed by no intestinal phosphate binder treatment for another 42 days (treatment group, n = 9) or no intestinal phosphate binder treatment for 84 days (control group, n = 8).
management of hyperphosphatemia in advanced stages of CKD. Specifically, ALOH is often used for the treatment for another 42 days (treatment group, n = 9) or no intestinal phosphate binder treatment for 84 days (control group, n = 8). *Denotes a significant difference in that group over time as assessed by the 2-way ANOVA (A) or the Friedman test (C). The color of the symbol denotes the treatment group it refers to.

Figure 4—Median daily food consumed (expressed as a percentage of daily food offered) (A) and median (IQR) body weight (B) and body condition score (C) in cats with surgically induced chronic kidney disease (n = 17), randomized to receive aluminum hydroxide (90 mg/kg/d, PO) for 42 days followed by no intestinal phosphate binder treatment for another 42 days (treatment group, n = 9) or no intestinal phosphate binder treatment for 84 days (control group, n = 8). *Denotes a significant difference in that group over time as assessed by the 2-way ANOVA (A) or the Friedman test (C). The color of the symbol denotes the treatment group it refers to.

Discussion

In accordance with our primary hypothesis, in this sample of young adult cats with induced CKD, the median serum FGF-23 concentration was higher than that of healthy, age-matched cats. This finding further confirms that this model of induced CKD shares similarities to naturally occurring CKD in cats.27 However, contrary to our secondary hypothesis, within the same sample, administration of ALOH for 6 weeks had no significant effect on serum phosphate or FGF-23 concentrations.

The induction of CKD and clinical course of the cats with induced CKD included in the study has been recently described.27 Specifically related to phosphorus balance, on average, the cats described here have historically had serum phosphate concentrations within the RI of the UGA Clinical Pathology Laboratory except in isolated episodes of acute deterioration of renal function in individual cats.27 The results of the study reported here confirm that most cats in the colony remain normophosphatemic, although concentrations are greater when compared to healthy cats, and a majority of cats had serum phosphate concentrations greater than ideal IRIS targets. This clinically aligns with the fact that a majority of these cats are in IRIS CKD stage 2 and chronically fed a phosphate-restricted diet.30 Similarly, given the known kidney dysfunction in this model, median FGF-23 concentrations in this group of cats were expected to be higher than in healthy cats due to the presumed associated phosphate retention. The results reported here are similar to serum FGF-23 concentrations in cats with naturally occurring CKD.27,28,30

Although not previously evaluated relative to changes in serum FGF-23 concentrations, the use of an IPB is common practice for the clinical management of hyperphosphatemia in advanced stages of CKD.24 Specifically, ALOH is often used for the objective evaluation of the efficacy of ALOH in cats with CKD has not yet been reported, and the lack of response to the administration of ALOH reported in this study was an unexpected finding.

Generally, IPBs are used to decrease the absorption of dietary phosphate with each meal by forming insoluble complexes that are excreted through feces31 without changing the nutritional composition of the diet.32 Similar to our results, a study32 performed to assess the efficacy of the IPB lanthanum carbonate octahydrate (Lantharenol; Bayer Animal Health) in healthy cats eating a maintenance diet showed no difference in serum phosphate concentrations between the treatment and control group or over time in the treatment group, but there was increased fecal excretion of phosphate. In the treatment group, there was a shift from urinary to fecal excretion of phosphate, which led to a decreased apparent digestibility of the dietary phosphate.32

Other IPBs have demonstrated clinical efficacy to reduce serum phosphate concentrations in healthy cats and cats with CKD.15–17 An IPB consisting of calcium carbonate and chitosan has been evaluated in several studies. In a trial done in 10 14-year-old cats with elevated plasma phosphate and urea concentrations being fed a maintenance diet, the digestibility of phosphate and plasma urea inorganic phosphate was significantly reduced after 35 days of treatment.33 Another study36 with a similar IPB (Epakitin; Vetoquinol USA) was performed in cats with induced CKD (IRIS stages 1 and 2) using an 11/12 nephrectomy model similar to that of the present study and consuming a maintenance diet.36 That study concluded that serum phosphate and plasma PTH concentrations were significantly lower in the treatment group compared to the control group after 56 days of supplementation. Additionally, lower serum phosphate and PTH concentrations were observed at 6 and 9 months compared to baseline, but values were no longer different from baseline after a 3-month washout period.36 A final IPB containing primarily calcium carbonate, calcium lactate, and chitosan (Renal P; Candioli Pharma) evaluated...
10 cats with IRIS stage 3 and 4 CKD eating a renal diet over 60 days and demonstrated a reduction of serum phosphate throughout all time points of the study.17 Another study18 evaluated the long-term supplementation with the same IPB in 20 cats with IRIS stage 3 and 4 CKD consuming a renal diet and concluded that the treatment group had reduced serum phosphate concentrations compared to historical control cats at all time points.

Although the influence of ALOH on FGF-23 has not been reported in any species, the authors of the present study expected to observe a decrease in serum FGF-23 concentrations with a reduction in absorbed dietary phosphate. Indeed, there is evidence in the literature that dietary phosphate directly influences FGF-23 concentrations in healthy people, mice, and cats.9,19-21 The effects of dietary phosphate loading on circulating FGF-23 occur independently of changes in the serum phosphate.19 A retrospective study20 concluded that FGF-23 concentrations decrease significantly in both hyperphosphatemic and normophosphatemic CKD cats after 4 weeks of consuming a renal diet, but plasma phosphate decreases significantly only in the hyperphosphatemic group. However, in the present study, serum FGF-23 concentrations did not decrease with ALOH treatment in the induced CKD cats. One possible explanation is that a subset of these cats had ionized and total hypercalcemia, which may be related to the fact that they were chronically fed a phosphate-restricted diet with a relatively high Ca:P ratio.40,41 The hypercalcemia might have prevented the expected decline in FGF-23 in response to ALOH as prior literature supports that tCa and iCa are independent predictors of circulating FGF-23 concentrations in cats with CKD, and hypercalcemia can increase FGF-23 concentrations independently of serum phosphate concentrations or glomerular filtration rate.14,16,42,43 It is also possible that our randomization procedures, which assigned cats with the highest serum phosphate and FGF-23 concentrations to the treatment group, inadvertently led to cats with more refractory phosphate retention being assigned to ALOH. Finally, as values of FGF-23 within the normal range or above 4,000 pg/mL are not reported by the commercial laboratory at which these samples were analyzed, a reduction in serum FGF-23 in cats with values < 300 pg/mL or > 4,000 pg/mL would not have been detected in this study, which represents an important limitation.

In human medicine, ALOH was first reported as an IPB in the early 1970s; however, it is rarely used in people today because of safety concerns related to the development of aluminum-induced microcytic anemia, seizures, and osteomalacia.44-46 To our knowledge, these complications have not been reported in cats given oral ALOH to treat hyperphosphatemia, although the inflammatory and mutagenic capacities of aluminum adjuvants have been studied in cats relative to vaccine-associated tumorigenesis.47,48

There are several limitations to the present study. Interpretation of the data presented here should be limited to the specific context and sample in the study, specifically a small number of younger cats with stable, mostly IRIS stage 2 CKD chronically fed a phosphate-restricted diet. Dietary phosphate restriction does have known efficacy in reducing serum phosphate and FGF-23 concentrations in cats with CKD.16 Cats were transitioned from dry food to wet food and had a 19-week acclimation period, but their food consumption was generally less with wet food than with the previously fed dry food. Although the ALOH was mixed well with each ration and the dose of ALOH prescribed was on the high end, it may be possible that cats consumed a smaller dose than was prescribed when their ration was not fully consumed. Another limitation was not measuring 1,25-hydroxyvitamin D in the healthy cat group or measuring the fecal phosphate excretion in the CKD group due to oversights in the study design. Finally, urinary excretion of phosphate was evaluated on single samples (not 24-hour urine collection); although phosphate excretion was indexed to that of creatinine, this might limit our ability to evaluate changes in phosphorous balance.

In conclusion, FGF-23 concentrations were elevated in this sample of cats with induced CKD. However, ALOH did not significantly reduce serum phosphate or FGF-23 concentrations in this small study of cats with surgically induced CKD chronically eating a phosphate-restricted diet.

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Supplementary Materials

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