Objective—To determine whether cats in the nonazotemic stages of chronic kidney disease have increased plasma parathyroid hormone (PTH) concentrations as a compensatory physiologic mechanism to maintain plasma phosphate concentration within the reference interval.

Design—Prospective longitudinal study.

Animals—118 client-owned geriatric cats with various degrees of renal function.

Procedures—For each cat, a blood sample was obtained for plasma biochemical analysis and determination of plasma PTH concentration, and a urine sample was obtained for determination of urine specific gravity at study entry (baseline) and after 12 months. For a subset of 30 cats, plasma calcitriol concentration was determined at baseline. Cats were categorized into 1 of 3 groups on the basis of kidney function at the end of 12 months. At baseline and after 12 months, plasma concentrations of variables associated with calcium homeostasis were compared between the 3 groups and also within groups over time. Multivariable linear regression was used to identify variables associated with plasma PTH concentration.

Results—Plasma PTH concentration was significantly increased in cats that developed azotemia, compared with PTH concentration in cats that remained nonazotemic, and PTH concentration increased before changes in plasma calcium and phosphate concentrations were detected. A moderate positive association between plasma calcitriol and PTH concentrations was identified. Plasma PTH concentration was associated with age and plasma urea, creatinine, and total calcium concentrations in the final multivariable model.

Conclusions and Clinical Relevance—Results suggested that renal secondary hyperparathyroidism can develop prior to azotemia in cats, even in the absence of hyperphosphatemia and hypocalcemia. (J Am Vet Med Assoc 2012;241:1326–1335)
PTH assays were developed to measure the concentration of the intact PTH molecule, the biologically active form of the hormone. Reference intervals for the concentration of the intact PTH molecule in cats were developed on the basis of results from 2 previous studies. Unfortunately, the PTH assays used to derive those reference intervals are no longer commercially available.

Vitamin D is an essential dietary nutrient for cats because they are unable to synthesize vitamin D via exposure to sunlight. Calcitriol is the active form of vitamin D. In patients with CKD, calcitriol concentrations may be decreased because of a reduction in dietary vitamin D intake and damage to or loss of nephrons that may be decreased because of a reduction in dietary vitamin D. In patients with CKD, calcitriol concentrations are decreased to the development of parathyroid gland hyperplasia, although calcitriol concentrations are decreased to the development of parathyroid gland hyperplasia, which results in continuous autonomous secretion of PTH. Although calcitriol concentrations are decreased in cats with advanced CKD, results of studies that involved cats with mild CKD indicate that those cats have calcitriol concentrations within the reference interval. However, the assays used to measure the calcitriol concentration in those studies are no longer commercially available.

Investigators of studies involving humans and rats with mild CKD report that affected patients have an increased PTH concentration in the absence of hypocalcemia and hyperphosphatemia. Investigators of another study involving dogs with IRIS stage 1 CKD reported that a significantly higher proportion of affected dogs have an increased PTH concentration, compared with the proportion of dogs that have hypocalcemia or hyperphosphatemia. Conversely, the direction of change in plasma calcitriol concentration varies among studies involving human and rodent patients with mild CKD. Plasma calcitriol concentration was decreased for patients with mild CKD in some studies whereas it remained within the reference interval for patients in another study. Generally, as GFR starts to decrease early in the course of CKD calcitriol concentration begins to decrease, which may initiate development of renal secondary hyperparathyroidism. Traditionally, the pathophysiologic mechanism for the development of renal secondary hyperparathyroidism in patients with CKD was believed to involve disturbances in calcium and phosphate homeostasis. However, multivariable analysis of data from studies involving human patients with CKD has identified additional nontraditional factors that are independently associated with increased plasma PTH concentrations such as body mass index, gender, age, and hypertension whereas smoking is associated with decreased plasma PTH concentrations.

To our knowledge, neither a study to evaluate calcium homeostasis in cats with CKD prior to the development of azotemia nor a study to evaluate the association of PTH concentration with nontraditional variables in cats with CKD has been performed. The objectives of the study reported here were to characterize biomarkers of renal function (plasma urea and creatinine concentrations and USG) and calcium and phosphate homeostasis (PTH, phosphate, and total calcium concentrations and calcium × phosphate product) as well as other variables such as age and SBP in cats in the nonazotemic and azotemic stages of CKD, compared with those in healthy geriatric cats; develop a multivariable model of variables (traditional and nontraditional) associated with plasma PTH concentration in cats with CKD; and report 95% confidence intervals for PTH and calcitriol concentrations in healthy geriatric cats. We hypothesized that plasma PTH concentrations would be increased in cats with CKD prior to the development of azotemia.

**Materials and Methods**

**Animals**—Clinically normal geriatric cats > 9 years of age with plasma creatinine concentrations < 2.0 mg/dL were recruited into a prospective longitudinal study from 2 veterinary practices in London. The study was approved by the Royal Veterinary College Ethics and Welfare Committee, and owner consent was obtained for all cats before study enrollment. A cat was excluded from the study if it had any concurrent medical disorder, had evidence of renal lymphoma, was fed a protein- or phosphate-restricted diet, or was receiving drugs known to affect calcium or phosphate homeostasis.

**Study design**—Study cats were monitored for 12 months. Each cat was categorized into 1 of 3 groups on the basis of results for plasma creatinine concentration and USG after 12 months. Group 1 included cats with a plasma creatinine concentration ≤ 1.6 mg/dL, group 2 included cats with a plasma creatinine concentration > 1.6 mg/dL and < 2.0 mg/dL, or a plasma creatinine concentration ≥ 2.0 mg/dL and a USG > 1.035, and group 3 included cats with a plasma creatinine concentration ≥ 2.0 mg/dL and a USG < 1.035 or persistent azotemia (plasma creatinine concentration ≥ 2.0 mg/dL on at least 2 consecutive visits a minimum of 14 days apart). Cats in groups 1 and 2 were considered nonazotemic, and cats in group 3 were considered azotemic. For a subset of 30 study cats (group 1, n = 9; group 2, 8; group 3, 13), plasma calcitriol concentrations were determined at study enrollment (baseline) only.

**Sample collection and laboratory evaluation**—From each cat, urine and blood samples were obtained at baseline and after 12 months. Urine samples were collected via cystocentesis, and USG was determined with a calibrated refractometer. Blood samples were collected via jugular venipuncture into blood collection tubes containing either sodium heparin or EDTA. All blood samples were obtained at mid to late morning to correspond with the nadir of PTH secretion, which, in humans, follows a circadian rhythm. Within 4 hours after collection, blood samples were centrifuged to obtain plasma. Plasma samples were frozen and stored at −80°C. Parathyroid hormone is heat labile; therefore, appropriate sample handling techniques were strictly followed.
Heparinized plasma samples were sent to a reference laboratory for biochemical analysis. Intact PTH concentration in EDTA-anticoagulated plasma samples was determined by means of a radioimmunoassay at a reference laboratory. Calcitriol concentration was determined by means of a radioimmunoassay at a different reference laboratory.

Nontraditional predictors of PTH concentration—For each cat, data for the following nontraditional variables that may affect PTH concentration were collected: age, sex, body weight, SBP, and exposure to cigarette smoke. Systolic blood pressure was measured via a Doppler technique as previously described. Data regarding exposure to cigarette smoke were collected via a standardized lifestyle questionnaire that was completed by the owners of study cats at enrollment.

Statistical analysis—Statistical analyses were performed with statistical software. Data were assessed for normal distributions via the Kolmogorov-Smirnov test and visual inspection of graphic plots. When necessary, a logarithmic transformation to the base 10 was applied to outcome variables that were measured on a continuous scale to normalize the distribution of the data so that linear regression could be performed. Otherwise, data were analyzed by the use of nonparametric testing as described. Variables were compared among the 3 groups at baseline and after 12 months via the Kruskal-Wallis test. Post hoc testing was performed via the Mann-Whitney U test with a Bonferroni correction used to adjust for multiple comparisons. For each classification group, changes in variables over time were evaluated via the Wilcoxon signed rank test. Correlations between variables were evaluated via the Spearman correlation coefficient.

A logarithmic to the base 10 transformation was applied to the data for plasma PTH concentration. Dependent variables considered in the models included age; sex; body weight; plasma creatinine, urea, phosphate, and total calcium concentrations; calcium × phosphate product; SBP; and exposure to cigarette smoke. Variables with a P < 0.10 on univariable analyses were eligible for consideration in a multivariable linear regression model, which was created by manual forward stepwise selection. Only variables with a P ≤ 0.05 were retained in the final multivariable regression model. Multicollinearity between various combinations of dependent variables was assessed by evaluation of the correlation matrix, variance inflation factor, and tolerance. Homoscedasticity of the multivariable model was evaluated by visual examination of a scatterplot of the standardized residuals versus the predicted values. The Durbin-Watson test was used to test correlation of adjacent residuals. Outlier and influential measures were identified via examination of leverage values and Cook’s distances, respectively.

A 95% confidence interval for the intact PTH assay was derived from the baseline PTH concentrations obtained from cats in group 1 and was defined by the 2.5th through 97.5th percentile of the data. A 95% confidence interval for the calcitriol assay was derived from the calcitriol concentrations obtained for 10 geriatric cats (these cats were considered healthy and had creatinine concentrations < 1.6 mg/dL and could be considered to be classified in group 1) that were not included in the present study and was defined by the 2.5th through 97.5th percentile of the data.

Results

Animals—One hundred eighteen cats were recruited into the study. After 12 months, 35 cats were categorized into group 1, 52 into group 2, and 31 in group 3. The median (range) age of cats in groups 1, 2, and 3 at study enrollment (baseline) was 13.3 years (9.0 to 21.8 years), 12.2 years (9.0 to 18.4 years), and 15.0 years (9.9 to 18.1 years), respectively. Of the cats that developed azotemia during the 12-month observation period (group 3), 30 were classified as having IRIS stage II CKD, and 1 was classified as having IRIS stage IV CKD.

Variable comparisons between groups—At baseline, the following variables differed significantly among the 3 groups: age (P = 0.007), plasma PTH concentration (P = 0.012), creatinine concentration (P < 0.001), urea concentration (P < 0.001), USG (P < 0.001), and SBP (P = 0.009; Table 1). Hypercalcemia (total calcium, > 11.8 mg/dL) was detected in 2 (5.7%) cats in group 1, 1 (1.9%) cat in group 2, and 0 cats in group 3, whereas hypocalcemia (total calcium, < 8.2 mg/dL) was not detected in any of the study cats. Hypophosphatemia (phosphate, < 2.8 mg/dL) was detected in 2 (5.7%) cats in group 1, 1 (1.9%) cat in group 2, and 2 (6.5%) cats in group 3, whereas hyperphosphatemia (phosphate, > 6.8 mg/dL) was not detected in any of the study cats. Hyperparathyroidism (PTH, > 265.2 mg/dL) was diagnosed in 0 cats in group 1, 4 (7.7%) cats in group 2, and 6 (19.4%) cats in group 3, whereas hypoparathyroidism (PTH, < 7.6 mg/dL) was not diagnosed in any of the study cats. Cats (group 3) that became azotemic during the study observation period had a significantly higher plasma PTH concentration at baseline, compared with that for cats in group 1 (Figure 1).

At the 12-month observation, the following variables differed significantly among the 3 groups: plasma phosphate concentration (P = 0.045), PTH concentration (P = 0.009), creatinine concentration (P < 0.001), urea concentration (P < 0.001), USG (P < 0.001), and SBP (P = 0.007; Table 1). Hypercalcemia was not detected in any of the study cats, and hypocalceemia was detected in only 1 (2.9%) cat in group 1. Hyperphosphatemia was detected in 1 (2.9%) cat in group 1, 0 cats in group 2, and 5 (16.1%) cats in group 3, whereas hypophosphatemia was detected in 1 (2.9%) cat in group 1, 2 (3.8%) cats in group 2, and 1 (3.2%) cat in group 3. Hyperparathyroidism was diagnosed in 0 cats in group 1, 3 (5.8%) in group 2, and 11 (35.5%) in group 3, whereas hypoparathyroidism was not diagnosed in any of the study cats. Cats (group 3) that became azotemic during the study observation period had a significantly higher plasma PTH concentration, compared with that for cats in groups 1 and 2 (Figure 1). For group 1, none of the variables evaluated changed significantly between baseline and the 12-month observation (Table 1). For group 2, the calcium × phosphate product at the 12-month observation was decreased

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**Table 1**—Median (range) values for variables associated with renal function at study enrollment (baseline) and after 12 months for 118 geriatric cats with various degrees of renal function and classified into 1 of 3 groups on the basis of results obtained after 12 months; group 1 (n = 35) included cats with a plasma creatinine concentration ≤ 1.6 mg/dL, group 2 (52) included cats with a plasma creatinine concentration > 1.6 mg/dL and < 2.0 mg/dL or a plasma creatinine ≥ 2.0 mg/dL and a USG > 1.035, and group 3 (31) included cats with a plasma creatinine concentration ≥ 2.0 mg/dL and a USG < 1.035 or persistent azotemia (plasma creatinine concentration ≥ 2.0 mg/dL on at least 2 consecutive observations a minimum of 14 days apart).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observation</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium (mg/dL)</td>
<td>Baseline</td>
<td>10.04 (8.92–12.48)</td>
<td>9.92 (8.88–13.32)</td>
<td>9.84 (8.92–11.44)</td>
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<td></td>
<td>12 mo</td>
<td>9.92 (6.0–11.88)</td>
<td>9.84 (8.88–11.0)</td>
<td>9.84 (8.26–11.76)</td>
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<tr>
<td>Phosphate (mg/dL)</td>
<td>Baseline</td>
<td>3.10 (2.07–5.91)</td>
<td>4.24 (2.54–6.38)</td>
<td>3.99 (2.07–6.38)</td>
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<tr>
<td></td>
<td>12 mo</td>
<td>3.90 (2.63–7.96)</td>
<td>4.02 (2.86–6.22)</td>
<td>4.46 (2.46–10.53)</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>Baseline</td>
<td>44.37 (7.62–265.22)</td>
<td>49.86 (9.41–465.66)</td>
<td>82.78 (14.11–3,269.24)</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>52.68 (9.41–205.08)</td>
<td>47.04 (12.23–708.37)</td>
<td>118.53 (12.23–4,424.99)</td>
</tr>
<tr>
<td>Calcium × phosphate product (mg²/dL²)</td>
<td>Baseline</td>
<td>40.60 (20.27–61.58)</td>
<td>42.82 (24.59–65.14)</td>
<td>39.56 (24.44–63.91)</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>38.44 (26.46–58.56)</td>
<td>39.56 (26.00–59.32)</td>
<td>45.20 (27.39–98.89)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Baseline</td>
<td>1.36 (1.00–1.57)</td>
<td>1.63 (1.29–1.99)</td>
<td>1.73 (1.07–1.98)</td>
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<tr>
<td></td>
<td>12 mo</td>
<td>1.36 (0.95–1.56)</td>
<td>1.65 (1.12–2.67)</td>
<td>2.19 (2.0–5.58)</td>
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<tr>
<td>Urea (mg/dL)</td>
<td>Baseline</td>
<td>26.61 (17.93–37.54)</td>
<td>30.11 (20.45–56.86)</td>
<td>37.54 (21.29–59.66)</td>
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<tr>
<td></td>
<td>12 mo</td>
<td>29.97 (17.85–39.22)</td>
<td>31.37 (19.33–66.50)</td>
<td>45.10 (29.41–104.5)</td>
</tr>
<tr>
<td>USG</td>
<td>Baseline</td>
<td>1.055 (1.014–1.086)</td>
<td>1.042 (1.016–1.086)</td>
<td>1.030 (1.014–1.080)</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>1.055 (1.014–1.086)</td>
<td>1.038 (1.010–1.080)</td>
<td>1.020 (1.013–1.055)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>Baseline</td>
<td>136.8 (113.6–210.0)</td>
<td>140.2 (101.8–217.6)</td>
<td>160.0 (116.8–241.2)</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>136.6 (100.4–192.8)</td>
<td>136.6 (105.2–180.5)</td>
<td>148.2 (113.5–253.2)</td>
</tr>
</tbody>
</table>

*Within a group, value differs significantly (P < 0.05) from that at baseline. †Within an observation, value differs significantly (P < 0.017; after Bonferroni adjustment) from that of group 1. ‡Within an observation, value differs significantly (P < 0.017; after Bonferroni adjustment) from that of group 2. Percillus id quam remanum idus et hili optatn nos iusquat.

Figure 1—Box-and-whiskers plot illustrating the PTH concentrations in geriatric cats with various degrees of renal function at study enrollment (baseline; A) and after 12 months (B). Group 1 (n = 35) included cats with a plasma creatinine concentration ≤ 1.6 mg/dL, group 2 (52) included cats with a plasma creatinine concentration > 1.6 mg/dL and < 2.0 mg/dL or a plasma creatinine ≥ 2.0 mg/dL and a USG > 1.035, and group 3 (31) included cats with a plasma creatinine concentration ≥ 2.0 mg/dL and a USG < 1.035 or persistent azotemia (plasma creatinine concentration ≥ 2.0 mg/dL on at least 2 consecutive observations a minimum of 14 days apart).

The 95% confidence interval for plasma PTH concentration that was derived significantly (P = 0.022), compared with that at baseline. For group 3, plasma creatinine concentrations increased (P < 0.001) and USG decreased (P = 0.001) significantly over time; this was expected because an increased creatinine concentration and decreased USG were inclusion criteria for this group. Additionally for group 3, plasma phosphate concentration (P = 0.035), urea concentration (P = 0.001), PTH concentration (P = 0.027), and calcium × phosphate product (P = 0.048) were significantly increased at the 12-month observation, compared with those at baseline.

Correlations between plasma PTH concentration and total calcium concentration and phosphate concentration were evaluated. At baseline, there was no correlation between plasma PTH and phosphate concentrations (r = 0.080; P = 0.390) and a weak inverse correlation between PTH and total calcium concentrations (r = −0.331; P < 0.001; Figure 2). Similarly, at the 12-month observation, there was no correlation between plasma PTH and phosphate concentrations (r = 0.050; P = 0.392) and a weak inverse correlation between PTH and total calcium concentrations (r = −0.283; P = 0.002).

**Plasma PTH concentration**—The 95% confidence interval for plasma PTH concentration that was derived
from the PTH concentrations of the 35 cats in group 1 was 7.6 to 265.2 pg/mL (0.8 to 27.9 pmol/L). Prior to linear regression analyses, a logarithmic transformation to the base 10 was performed on plasma PTH concentration data because the data were not normally distributed. On the basis of results of univariable analyses, the following predictor variables were associated with plasma PTH concentration and met the criterion (P < 0.10) for consideration in the multivariable model: age (P < 0.001), body weight (P = 0.007), plasma creatinine concentration (P = 0.001), phosphate concentration (P = 0.093), total calcium concentration (P < 0.001), urea concentration (P < 0.001), and SBP (P = 0.054). The final multivariable linear regression model included total calcium concentration (P < 0.001), age (P = 0.007), urea concentration (P = 0.008), and creatinine concentration (P = 0.029; Table 2).

Plasma calcitriol concentration—The 95% confidence interval for plasma calcitriol concentration that was derived from the plasma calcitriol concentrations of 10 healthy geriatric cats that were not included in the present study was 20.8 to 65.0 pg/mL (54.0 to 169.0 pmol/L). Comparisons of plasma calcitriol concentration among the classification groups were not performed because the number of cats evaluated in each classification group was considered too small to make any meaningful comparisons. The Spearman correlation coefficient indicated a positive correlation between plasma PTH and calcitriol concentrations (r = 0.581; P = 0.001).

**Discussion**

In the present study, 35.5% (11/31) of cats that developed azotemia (group 3) during the observation period had elevated PTH concentrations at the 12-month observation. Investigators of a previous study reported that the prevalence of hyperparathyroidism in cats with CKD was 84% (67/80), with 7 of 13 cats in the early stages (azotemia with no clinical signs) of CKD having increased PTH concentrations. In the present study,
PTH was increased in nonazotemic cats that subsequently developed azotemia within 12 months without detectable differences in phosphate or total calcium concentrations between the groups. This novel finding in cats is consistent with those of studies\(^\text{15–18}\) conducted with human patients in the early stages of CKD. It is likely that the increased PTH concentration in cats with CKD is a compensatory mechanism that enables affected cats to maintain a clinically normal plasma phosphate concentration via decreased renal reabsorption of filtered phosphate and increased renal excretion of phosphate. To confirm this hypothesis, renal excretion of phosphate should be measured via collection of 24-hour urine samples from cats with concurrent CKD and increased PTH concentrations. At the 12-month observation, the median concentrations of plasma phosphate and PTH were significantly increased in cats that had developed azotemia, compared with cats that remained nonazotemic; however, many (25/31 [81%]) of those azotemic cats had plasma phosphate concentrations that were within the reference interval. As CKD progresses, functional renal mass decreases and phosphate excretion is limited by an ever-decreasing GFR because there is no secretory pathway for phosphate in the kidney tubules. Subsequently, phosphate retention will cause an increased plasma phosphate concentration if dietary phosphate intake remains the same.

In the present study, the correlation between PTH and phosphate concentrations was not significant at either observation (baseline and at 12 months), whereas there was only a weak inverse correlation between PTH and total calcium concentrations at both baseline and the 12-month observation. This suggests that variables other than plasma total calcium concentration and phosphate concentration may be involved in the regulation of plasma PTH concentration. A low calcium concentration stimulates PTH secretion via the calcium-sensing receptor.\(^2\) In the present study, the correlations between PTH and total calcium concentrations were weak at baseline and after 12 months, and the total calcium concentrations did not differ significantly among groups at baseline or after 12 months. Total calcium concentration consists of 3 fractions: ionized calcium, protein-bound calcium, and complexed calcium, in which calcium is bound to an anion such as bicarbonate, citrate, lactate, or phosphate. Total calcium concentration is an imprecise indicator of ionized calcium concentration. Ionized calcium is the biologically available form of calcium; therefore, it is more likely to have a stronger association with PTH for maintaining calcium homeostasis. A limitation of the present study was that ionized calcium concentration was not measured because the clinics where the study cats were examined did not have access to the specialized equipment necessary to measure ionized calcium concentration. In a study\(^\text{19}\) that involved cats with CKD, total calcium concentration was an inaccurate measure for assessing ionized calcium concentration in 40% of the study population. Impaired kidney function can result in increased concentrations of anions such as phosphate and lactate, which then bind to ionized calcium, thereby increasing the complexed calcium fraction and decreasing the ionized calcium fraction of the total calcium concentration. An increase in total calcium may be seen if there is a substantial increase in the complexed calcium fraction.

It has been hypothesized that decreased calcitriol concentration is involved in the development of renal secondary hyperparathyroidism in patients in the early stages of CKD.\(^\text{15–17,19}\) Nonetheless, in the present study, there was a significant positive correlation between plasma PTH and calcitriol concentrations as determined at baseline for a subset of the study cats. This positive correlation may be expected because the normal physiologic response to an increased PTH concentration is stimulation of calcitriol synthesis. The positive correlation between PTH and calcitriol concentration in the present study suggests that the capacity of renal tubules to synthesize calcitriol was not affected in cats in the nonazotemic stages of CKD. However, because of the large volume of plasma required for the calcitriol assay, the calcitriol concentration was determined for only a small number of cats in each group; therefore, these results should be interpreted with caution. Moreover, the role of calcitriol deficiency in the pathophysiology of renal secondary hyperparathyroidism remains unclear and warrants further study.

Hypercalcemia that results from autonomous secretion of PTH may contribute to soft tissue calcification. Soft tissue calcification can develop when the calcium \(\times\) phosphate product becomes abnormally increased (ie, > 70 mg\(^2/dL\)).\(^8\) In the present study, 5 of 31 (16%) azotemic cats had calcium \(\times\) phosphate products > 70 mg/dL, whereas none of the nonazotemic cats had an abnormally increased calcium \(\times\) phosphate product. We were unable to assess soft tissue calcification in the present study because diagnostic imaging or collection of biopsy specimens from the study cats was not routinely performed.

The 95% confidence interval for plasma PTH concentration for the clinically normal geriatric cats (group 1) in the present study was 7.6 to 265.2 pg/mL, and the median was 44.4 pg/mL. The first reference interval established for PTH concentration in cats was 2.8 to 25.4 pg/mL,\(^1\) and that recommended by investigators of a later report\(^2\) was 7.7 to 43.3 pg/mL. The assays used to determine PTH concentration in those studies\(^\text{1,11}\) are no longer commercially available; therefore, a reference interval for PTH concentration in cats as determined by a currently available PTH assay is necessary. The range of plasma PTH concentrations for the group 1 cats of the present study was much wider than either established reference interval. This may have been caused by differences in the respective study populations. Investigators of the previous studies\(^\text{1,11}\) established their respective reference intervals on the basis of PTH concentration results obtained from healthy adult cats, whereas the confidence interval reported here was derived from the PTH concentration results obtained from healthy geriatric cats. The older mean age of the cats in the present study may have contributed to generally higher PTH concentrations and a wider range for PTH concentrations within the study population, compared with the previously established reference intervals. Results of studies\(^\text{21,22}\) involving human patients indicate that PTH...
concentration increases with age, and age was significantly associated with PTH concentration in the present study. Differences in sample type may be another reason for the PTH concentration range for group 1 cats of the present study to vary from the established reference intervals for PTH concentration in cats. Parathyroid hormone concentration was measured in serum in one of the studies,\(^\text{17}\) whereas it was measured in plasma obtained from EDTA-anticoagulated blood samples in the present study. In humans, PTH concentrations were approximately 10% to 30% higher in plasma obtained from EDTA-anticoagulated blood samples, compared with that in serum samples.\(^\text{29}\) It is common for results obtained from different PTH assays to vary within and across species. Although the reason for this variability remains unclear, it may be associated with variations in the extent to which different assays measure PTH fragments in addition to the intact PTH molecule.\(^\text{29}\) Carboxy-terminal PTH fragments can accumulate in patients with CKD; therefore, in such patients, it is important that PTH concentration is measured via an assay that detects the intact PTH molecule. It has been suggested that second-generation intact PTH assays may also detect a PTH fragment (7–84 PTH) to varying extents,\(^\text{29}\) and cross-reactivity with 7–84 PTH may be another explanation for the differing reference intervals for PTH concentration in cats. Third-generation intact PTH assays have been developed, and a recent publication reported the validation of their use for the measurement of PTH concentrations in cats.\(^\text{10}\) The number of cats in group 1 (n = 35) in the present study was very small; therefore, it was not possible to determine a reference interval but only a 95% confidence interval. It is recommended that a minimum of 120 individuals be used when establishing reference intervals.\(^\text{11}\) The 95% confidence interval for calcitriol concentration derived from 10 healthy geriatric cats not included in the present study was 20.8 to 65.0 pg/mL. This was similar to the reference interval (9.0 to 57.0 pg/mL) for calcitriol concentration in cats reported by investigators of another study\(^\text{1}\) as well as the reference interval (15.4 to 57.7 pg/mL) for calcitriol concentration in humans provided by the laboratory\(^\text{4}\) that performed the assay.

Variables associated with plasma PTH concentration identified via multivariable linear regression analysis were age and plasma total calcium, urea, and creatinine concentrations. Age and urea and creatinine concentrations were positively correlated with PTH concentration. Conversely, total calcium concentration was negatively correlated with PTH concentration. The overall predictive value of the model was only moderate (R\(^2\) = 0.344), which suggests that plasma PTH concentration is also affected by additional unmeasured and unidentified variables. Urea and creatinine concentrations are biomarkers for kidney function. As kidney function deteriorates, PTH concentration increases as a compensatory mechanism to try to maintain phosphate concentrations within clinically normal limits. Thus, it was expected that increased urea and creatinine concentrations would be associated with a concurrent increase in PTH concentration. The fact that PTH concentration increased as total calcium concentration decreased was also expected because a low calcium concentration stimulates PTH secretion.\(^\text{2}\) In humans, PTH concentration tends to increase as patients age.\(^\text{21,22}\) Similarly, in the present study, an increase in age was associated with an increase in PTH concentration. This finding is important to note considering that the cats in the azotemic group (group 3) had the highest median PTH concentration as well as the highest median age. Further research, in which azotemic cats with CKD are age matched with clinically normal control cats, is necessary to determine whether age is an independent or confounding factor associated with an increased PTH concentration.

In the final multivariable linear regression model of the present study, body weight was not associated with plasma PTH concentration. Conversely, in studies\(^\text{21,23}\) involving human patients, a positive association between PTH concentration and body mass index has been identified. The reason for the conflicting results regarding the association between PTH concentration and body weight or body mass index may be that the patients in the human studies\(^\text{21–23}\) had CKD, whereas the majority (87/118) of patients in the present study were either clinically normal or in the early, nonazotemic stage of CKD.

Smoking was associated with decreased PTH concentration in previous large-scale epidemiological studies\(^\text{22,24,25}\) involving humans. It is believed that cigarette smoke has a direct toxic effect on the parathyroid gland, which impairs PTH synthesis.\(^\text{22,24,25}\) For the cats in the present study, exposure to cigarette smoke was not associated with an increase in plasma PTH concentration. To our knowledge, the effect of passive smoke on PTH concentrations in humans has not been investigated. Results of a study\(^\text{32}\) conducted to investigate the effects of passive smoke exposure on parathyroid gland function in hamsters indicate that passive smoke increases the cellular activity of the parathyroid gland.

In studies\(^\text{22,24,35–37}\) involving human patients, blood pressure was positively associated with PTH concentration. Moreover, chronic administration of PTH to healthy humans has been associated with the development of hypertension.\(^\text{38}\) The mechanism by which PTH induces hypertension is not completely understood; however, PTH has various effects on vascular smooth muscle cells that could contribute to hypertension.\(^\text{39}\) In the present study, 31 of 118 (26%) cats were classified as hypertensive (SBP > 160 mm Hg and concurrent hypertensive retinal lesions). In the univariable linear regression model, SBP was positively associated with PTH concentration; however, SBP was not retained in the final multivariable linear regression model.

Results of the present study suggested that additional variables may be associated with the development of increased PTH concentration in cats with CKD. One such variable may be magnesium concentration. In human patients, there is a negative correlation between magnesium and PTH concentrations that is independent of calcium and phosphate concentrations.\(^\text{40}\) In a study\(^\text{40}\) that involved cats that had received renal transplants, hypomagnesemia was detected in 13 of 14 cats; therefore, ionized magnesium concentration should be considered in future studies of renal secondary hyper-
parathyroidism in cats. Another variable that may be associated with PTH homeostasis is expression of the calcium-sensing receptor. Results of a study involving human patients with renal secondary hyperparathyroidism indicate that affected patients had decreased expression and function of the calcium-sensing receptors, which was associated with increased cellular proliferation within the parathyroid gland. The calcium-sensing receptor has recently been identified and sequenced in cats, and further research is necessary to determine whether expression of the calcium-sensing receptor is also altered in cats with CKD and renal secondary hyperparathyroidism. Fibroblast growth factor-23 may be another variable that may contribute to the development of renal secondary hyperparathyroidism. Fibroblast growth factor-23 is involved in phosphate homeostasis and aids in the regulation of phosphate excretion by the kidneys; it also inhibits 1-α-hydroxylase activity in the kidneys, which consequently decreases calcitriol concentration. Fibroblast growth factor-23 concentrations increase with declining renal function, and an increased concentration of FGF-23 is one of the earliest detectable abnormalities in human patients with CKD and precedes changes in calcium and phosphate concentrations. Additionally, an increased FGF-23 concentration may contribute to decreased calcitriol concentration, which in turn contributes to the development of renal secondary hyperparathyroidism. A positive correlation between FGF-23 and PTH concentrations has been identified in healthy humans as well as human patients with CKD. Measurement of FGF-23 concentration in cats with various stages of CKD may aid in elucidating the pathophysiologic changes of renal secondary hyperparathyroidism.

Results from the present study suggested that measurement of PTH concentration may be beneficial for the management of cats that are at risk for developing azotemia, and interventional studies to evaluate the effects of appropriate management of renal secondary hyperparathyroidism in such cats are warranted. Management of renal secondary hyperparathyroidism in cats generally focuses on the control of hyperphosphatemia via a reduction in dietary intake of phosphates. Some clinicians advocate oral administration of calcitriol to decrease PTH concentration. Results of an uncontrolled survey indicate that daily oral administration of low doses of calcitriol was safe and effective for the control of renal secondary hyperparathyroidism in cats with CKD; however, results of another study indicate that following calcitriol administration, PTH concentration did not significantly differ between clinically normal cats and cats with CKD. Moreover, calcitriol administration is accompanied by a substantial risk for the development of hypercalcemia and hyperphosphatemia; therefore, in human patients, the use of calcimimetics is being explored for management of renal secondary hyperparathyroidism. Calcimimetics mimic the effects of extracellular calcium and increase activation of the calcium-sensing receptors, which in turn inhibits PTH release from the parathyroid gland. To our knowledge, no study has been conducted to evaluate the effectiveness of calcimimetics for the management of renal secondary hyperparathyroidism in cats.

Phosphate binders are effective in controlling hyperphosphatemia and are used for the management of renal secondary hyperparathyroidism in patients with CKD. For human patients with CKD and phosphate concentrations within reference limits, administration of a phosphate binder not only maintained phosphate concentration within reference limits, but also reduced PTH and FGF-23 concentrations. Randomized controlled clinical trials need to be conducted with cats to determine whether dietary protein restriction and the administration of calcitriol, calcimimetics, and phosphate binders during the early stages of CKD are beneficial in preventing the development of renal secondary hyperparathyroidism.

The present study had some limitations. It is possible that the increased PTH concentration in some of the study cats was the result of primary hyperparathyroidism. Primary hyperparathyroidism could not be ruled out because histologic examination of parathyroid glands was not performed, but it is rare in cats, and clinical findings in the study cats were not suggestive of primary hyperparathyroidism. Another limitation of the present study was that only the concentration of calcitriol (1,25(OH)2 D3) was measured; the concentration of calcidiol (25(OH)D3), the nutritional form of vitamin D, was not measured. The measurement of calcidiol concentration would have allowed us to determine whether the decreased calcitriol concentrations were the result of decreased dietary intake of vitamin D or a pathophysiologic consequence of CKD. We were also unable to measure the ionized calcium (the biologically active form of calcium) concentrations in the study cats; therefore, we do not know whether any of the cats had a biologically relevant hypocalcemia (ie, decreased ionized calcium concentration). Finally, the study population of cats, particularly that for which calcitriol concentration was measured, was small, and a larger population would have improved the power of the study.

Although multiple studies have been conducted to evaluate changes in calcium and phosphate homeostasis in cats with azotemic CKD, to our knowledge, the present study is the first to also evaluate PTH, calcium, phosphate, and calcitriol concentrations in cats that are in the early nonazotemic stages of CKD. Measurement of plasma PTH concentration is recommended for cats that are suspected of having, or considered at risk for developing, CKD. Early detection of increased PTH concentrations may allow clinicians to implement interventions aimed at reducing PTH concentrations, which may prevent or slow the development of renal secondary hyperparathyroidism. The present study was also the first to use multivariable analysis to identify variables associated with PTH concentration in cats. This information is important in elucidating the pathophysiology of renal secondary hyperparathyroidism. Future studies are required to evaluate the effects that early intervention to manage renal secondary hyperparathyroidism may have on the progression of CKD and survival time in affected cats.

The present study revealed that plasma PTH concentration is increased in cats prior to the development of azotemia, compared with that in cats remaining nonazotemic in the absence of a concurrent decrease in
total calcium concentration and increase in phosphate concentration, which suggests that hypocalcemia and hyperphosphatemia may not be substantial factors in the development of renal secondary hyperparathyroidism. The importance of calcitriol concentration on PTH concentration and the development of renal secondary hyperparathyroidism in cats with CKD remains unclear.

References

From this month’s AJVR

Effects of anesthetic drugs on canine splenic volume determined via computed tomography
Caroline F. Baldo et al

Objective—To evaluate effects of commonly used anesthetics administered as single bolus injections on splenic volume.

Animals—10 adult Beagles.

Procedures—A randomized crossover study was conducted. Computed tomography was performed on dogs to determine baseline splenic volume and changes after IV injection of assigned drug treatments. Dogs were allowed to acclimate for 10 minutes in a plastic crate before acquisition of abdominal CT images. Treatments were administered at 7-day intervals and consisted of IV administration of saline (0.9% NaCl) solution (5 mL), acepromazine maleate (0.03 mg/kg), hydromorphone (0.1 mg/kg), and dexmedetomidine (0.005 mg/kg) to all 10 dogs; thiopental (8 mg/kg) to 5 of the dogs; and propofol (5 mg/kg) to the other 5 dogs. Splenic volume was calculated from the CT images with image processing software. A repeated-measures ANOVA was performed, followed by a Bonferroni post hoc test.

Results—No significant difference in splenic volume was detected between the acepromazine, propofol, and thiopental treatments, but splenic volume was greater with these drugs than with saline solution, hydromorphone, and dexmedetomidine. Splenic volume was less with hydromorphone, compared with dexmedetomidine, but splenic volume with hydromorphone and dexmedetomidine did not differ significantly from that with saline solution.

Conclusions and Clinical Relevance—Administration of acepromazine, thiopental, and propofol resulted in splenomegaly. Dexmedetomidine did not alter splenic volume. Hydromorphone slightly decreased splenic volume. Propofol should not be used when splenomegaly is not desirable, whereas hydromorphone and dexmedetomidine may be used when it is best to avoid splenic enlargement. (Am J Vet Res 2012;73:1715–1719)