AJVR

AVMA

Urinary angiotensinogen indexed to creatinine or protein is higher in cats with surgically induced chronic kidney disease compared to healthy cats

Jane H. C. Huang, DVM, MSc; Bianca N. Lourenço, DVM, PhD, DACVIM*; Chad W. Schmiedt, DVM, DACVS

Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA

*Corresponding author: Dr. Lourenço (lourenco@uga.edu)

Objective
To compare urinary angiotensinogen, a proposed biomarker for intrarenal renin-angiotensinogen system (RAS) activity, between cats with surgically induced chronic kidney disease (CKD) and healthy cats and explore its correlation with select clinical and circulating renin-angiotensin-aldosterone system (RAAS) markers.

Methods
Urine was banked from September 2022 through April 2023 during a study comparing circulating RAAS markers between cats with induced CKD and sex- and life stage–matched healthy cats. Urinary angiotensinogen concentration was measured from October 2025 through July 2026 using a validated in-house ELISA. Urinary concentration of angiotensinogen was indexed to that of creatinine or protein to account for urine concentration or indiscriminate urinary protein loss, respectively.

Results
28 cats (n = 14/group) were included. The median (IQR) indexed urinary angiotensinogen was higher in cats with CKD than in healthy cats (urinary angiotensinogen-to-protein ratio, 9.80 [5.47, 17.22] vs 3.38 [1.09, 5.52]; urinary angiotensinogen-to-creatinine ratio, 0.99 [0.40, 2.34] vs 0.31 [0.21, 0.60]). In cats with CKD, indexed urinary angiotensinogen correlated positively with serum creatinine concentration (urinary angiotensinogen-to-protein ratio, ρ = 0.573; urine angiotensinogen-to-creatinine ratio, ρ = 0.642). In healthy cats, urinary angiotensinogen-to-creatinine ratio correlated negatively with several circulating RAAS markers, including serum angiotensin II (ρ = −0.547) and angiotensin 1-7 (ρ = −0.631) equilibrium concentrations.

Conclusions
The intrarenal RAS, assessed by urinary angiotensinogen, is activated in cats with induced CKD, and its activity is inversely related to that of the circulating RAAS in healthy cats but not those with CKD.

Clinical Relevance
Concurrent evaluation of circulating RAAS and intrarenal RAS markers is required for complete assessment of this system.

Keywords: intrarenal renin-angiotensin system, circulating renin-angiotensin-aldosterone system, enzyme-linked immunosorbent assay (ELISA), amlodipine, urinary biomarker

Chronic kidney disease (CKD) is among the most common conditions affecting senior cats, impacting quality of life and survival.[1,2] Overactivation of the renin-angiotensin-aldosterone system (RAAS), a key regulator of vascular tone and extracellular fluid volume and composition, contributes to CKD progression and development of systemic arterial hypertension.[3–6] In addition to the important physiologic and pathophysiologic roles of the historically described circulating RAAS, recent studies[7–9] increasingly highlight the roles of an intrarenal, paracrine/autocrine renin-angiotensin system (RAS) regulated at the tissular level; this is now widely known as the intrarenal RAS.

Direct evaluation of the intrarenal RAS requires renal tissue, sampling of which relies on renal biopsy or postmortem sample collection, which has been a major obstacle for relevant research. In the field of human medicine, the urinary concentration of angiotensinogen, the only known precursor

Received June 15, 2026
Accepted August 11, 2026
Published online August 27, 2026

doi.org/10.2460/ajvr.26.06.0262

© 2026 THE AUTHORS. Published by the American Veterinary Medical Association as an Open Access article under Creative Commons CCBY-NC license.

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

protein of angiotensin and possibly the rate-limiting factor of the intrarenal RAS,[7] has been proposed as the most promising noninvasive biomarker for intrarenal RAS.[7,10] In humans, urinary angiotensinogen is positively correlated with intrarenal angiotensin II immunostaining[11–16] and inversely correlated with kidney function.[17,18] Further, urinary angiotensinogen predicts the risk of kidney function deterioration in patients with immunoglobulin A (IgA) nephropathy[19] or CKD of various etiologies.[12] These data have enabled researchers to use urinary angiotensinogen as a surrogate for intrarenal RAS activity in humans, although debate remains over whether the urinary angiotensinogen elevation observed in patients merely reflects an overall increase in urinary protein loss.[20,21]

Information on the intrarenal RAS in cats remains limited and restrained by the need for tissue samples. Two earlier studies[22,23] assessing RAS components in kidney tissue using immunohistochemistry staining reported mixed results on intrarenal RAS activation in cats with impaired kidney function. However, relevant medical history, including diet, systemic arterial blood pressure, and whether the cats were administered RAAS-modifying drugs, was not described. Two more recent studies[24,25] assessed the intrarenal RAS through kidney tissue mRNA levels of relevant genes (eg, angiotensinogen and renin). Both studies identified a higher angiotensinogen mRNA level in cats with kidney disease compared to healthy cats. Further, post hoc analysis from one of these studies[25] found a positive association between angiotensinogen mRNA level and the equilibrium concentration of angiotensin II in the kidneys of cats.[26] Notably, the corresponding urinary angiotensinogen concentration was not determined as the methodology to measure urinary angiotensinogen was not available when these studies were conducted.

An in-house ELISA that quantifies feline angiotensinogen in urine was recently developed and validated.[26] This study aimed to compare urinary angiotensinogen in cats with surgically induced CKD and in sex- and life stage–matched healthy cats. Given its proposed role as an indicator of intrarenal RAS, we also investigated correlations between urinary angiotensinogen and select clinical and circulating RAAS markers.

Methods

Study design

This was a retrospective study using data and urine samples banked from a previous study[27] that aimed to characterize the circulating RAAS in cats with surgically induced CKD. In that study, the circulating RAAS was evaluated via measurement of serum equilibrium concentrations of various angiotensin peptides (ie, angiotensin I, II, III, IV, 1-5, and 1-7) and aldosterone using LC-MS-MS. Urine samples collected during that study were banked at −80 °C for future analyses. Clinical, clinicopathologic, and circulating RAAS data generated in the previous study were reviewed, and banked urine samples were used for urinary angiotensinogen, protein, and creatinine analyses.

Animals

Cats in the surgically induced CKD group were purpose bred and underwent an 11/12th functional nephrectomy from January through July, 2019, as previously described.[28] At the time of evaluation for the parent study[27] and urine collection (April 10 through 17, 2023), all cats in the CKD group were clinically stable, with 6 out of 14 cats having a previous diagnosis of systemic arterial hypertension chronically treated with amlodipine besylate (0.625 to 2.5 mg/cat, PO, once a day). All procedures of the original study were approved by the University of Georgia IACUC (animal use protocol No. A2018 10–001) and the Clinical Research Committee of the University of Georgia College of Veterinary Medicine (approval No. CR-665).

Cats in the control group were owned by staff members or students of the University of Georgia Veterinary Teaching Hospital and were recruited from September 9 through December 14, 2022.[27] These cats were recruited to match the CKD group's sex proportion and life stage (ie, young adult). They were considered healthy based on a detailed medical history, physical examination, systolic blood pressure (SBP) measurement (indirectly obtained via Doppler sphygmomanometry), and clinicopathological evaluation, including hematology and serum and urine analyses. Informed owner consent was obtained prior to enrollment.

All cats whose urine samples were available were included in this study.

Sample analysis

Urinary total protein, creatinine, and angiotensinogen concentrations were measured on thawed urine samples from October 28 through November 11, 2025. Total protein and creatinine concentrations were measured by the Clinical Pathology Laboratory of the University of Georgia College of Veterinary Medicine using enzymatic and turbidimetric methods, respectively. Urinary angiotensinogen concentration was measured using a previously developed in-house sandwich ELISA.[26] All standards (recombinant feline angiotensinogen) and samples were run in triplicate, and the average of the 3 measurements was used.

Statistical analysis

Statistical analysis was conducted using the open-source software R (version 4.5.1; R Foundation for Statistical Computing).[29]

Data distribution for each variable was inspected visually and through the Shapiro-Wilk test and deemed unlikely to have followed normal distributions. Therefore, data are presented as median (1st quartile, 3rd quartile), and comparisons were conducted using the Mann-Whitney *U* test. Urinary angiotensinogen concentrations (expressed in ng/mL) were indexed to those of urinary creatinine or urinary total protein (both expressed in mg/dL)

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

to account for overall urine concentration or the indiscriminatory urinary protein loss, respectively. The ability of indexed urinary angiotensinogen or urinary protein-to-creatinine ratio (UPC) to distinguish between cats with CKD and healthy cats was further examined using receiver operating characteristic curves; the optimal cutoff was determined by maximizing the sum of sensitivity and specificity (Youden index).

The correlations between indexed urinary angiotensinogen or UPC and selected clinical and circulating RAAS markers were examined using Spearman correlation analysis. Clinical variables included serum creatinine concentration, SBP, and UPC. Circulating RAAS markers included serum equilibrium concentrations of angiotensin II, angiotensin 1-7, and aldosterone, as well as surrogates for ACE activity (ACE-S) and plasma renin activity (PRA-S). As described in the previous publication,[27] these surrogates were calculated using previously described formulas:

ACE-S ([pmol/L]/[pmol/L]) = (angiotensin II)/(angiotensin I)[30]

PRA-S (pmol/L) = (angiotensin I) + (angiotensin II)[31]

For all inferential statistics, *P* values < .05 were defined as significant.

Results

Animals

Fourteen cats with surgically induced CKD and 14 healthy cats had urine samples available and were included in this study. The demographic data at the time of urine sample collection are summarized in **Table 1**. All cats from both groups were in the same life stage (young adult) according to the

Table 1—Baseline demographic and clinical characteristics of cats with surgically induced chronic kidney disease (CKD) and sex- and life stage–matched healthy cats.

	Control (n = 14)	CKD (n = 14)	*P* value
Age (y)	3.34 (2.43, 3.55)	5.08 (5.05, 5.10)	< .001†
Body weight (kg)	4.44 (4.20, 5.20)	4.01 (3.35, 4.14)	.001‡
Sex			N/A*
Female, spayed	8 (57.1%)	8 (57.1%)	
Male, neutered	6 (42.9%)	6 (42.9%)	
Systolic blood pressure (mm Hg)	121 (109, 132)	143 (140, 171)	< .001†
Hct (%)	38.8 (34.9, 41.8)	36.1 (33.5, 38.5)	.141
Serum creatinine (mg/dL)	1.45 (1.20, 1.58)	2.05 (1.92, 2.35)	N/A*
Serum SDMA (µg/dL)	11.5 (10.0, 12.8)	Not performed	N/A
Serum urea nitrogen (mg/dL)	22.5 (20.2, 26.0)	22.0 (21.2, 25.5)	N/A*
Serum potassium (mmol/L)	4.30 (4.12, 4.60)	4.60 (4.00, 4.77)	.746
Serum phosphorus (mmol/L)	4.15 (3.62, 4.50)	3.50 (3.23, 3.68)	.020‡
Urine specific gravity	1.05 (1.05, 1.05)	1.03 (1.02, 1.04)	N/A*
Urinary protein (mg/dL)	33.5 (29.0, 45.5)	23.5 (15.2, 36.2)	.043‡
Urinary creatinine (mg/dL)	305 (261, 353)	222 (134, 299)	.066
UPC	0.11 (0.09, 0.16)	0.11 (0.07, 0.14)	.504
Urinary angiotensinogen (ng/mL)	92.9 (62.4, 195)	166 (109, 459)	.089
Urine angiotensinogen-to-creatinine ratio (10^{-4})	0.31 (0.21, 0.60)	0.99 (0.40, 2.34)	.031‡
Urine angiotensinogen-to-protein ratio (10^{-4})	3.38 (1.09, 5.52)	9.80 (5.47, 17.22)	.003†

Data are presented as median (1st quartile, 3rd quartile) or n (%) as appropriate. *P* values were computed with the Mann-Whitney *U* test.

**P* values were not computed since the variable was part of the grouping definition (eg, serum creatinine, SDMA, and BUN) or matching criteria (eg, sex). †*P* < .01. ‡*P* < .05.

N/A = Not applicable. SDMA = Symmetric dimethylarginine. UPC = Urinary protein-to-creatinine ratio.

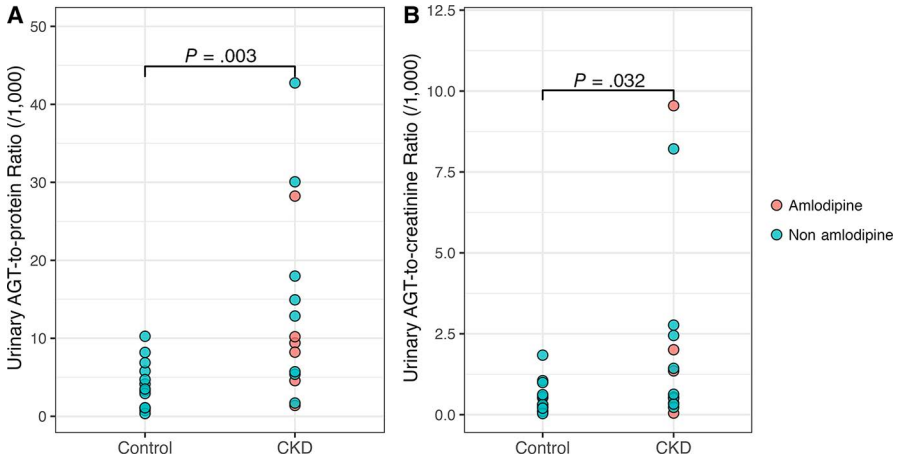


Figure 1—Dot plot of urinary angiotensinogen (AGT)-to-protein ratio (A) and urinary AGT-to-creatinine ratio (B) in cats with surgically induced chronic kidney disease (CKD; n = 14) and sex- and life stage–matched healthy cats (n = 14). Six of 14 cats in the group CKD were receiving amlodipine at the time of sampling and are marked in pink. *P* values were computed using the Mann-Whitney *U* test.

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

American Animal Hospital Association and the American Association of Feline Practitioners guidelines.[32] There was no correlation between urinary angiotensinogen and age for both the control and CKD groups **(Supplementary Figure S1)**.

Thirteen cats in the CKD group were in International Renal Interest Society CKD stage 2, and 1 was in stage 3. Twelve cats were not proteinuric (UPC < 0.2), and 2 cats were borderline proteinuric (UPC > 0.2 and < 0.4). Six cats were systemically hypertensive and undergoing amlodipine treatment (0.625 to 2.5 mg/cat, PO, once a day), 6 cats were prehypertensive, and 2 cats were normotensive.[33] As described in detail in the parent study,[27] all but 1 cat with CKD were fed a therapeutic renal diet (Hill's Prescription Diet k/d with Chicken Dry Cat Food; sodium content, 57 mg/100 kcal); 1 cat was fed a hypoallergenic commercial diet with low sodium content (Hill's Prescription Diet z/d; sodium content, 79 mg/100 kcal). All but 1 cat in the control group were fed a maintenance diet (sodium content, 101 to 250 mg/100 kcal); 1 cat was fed a low-sodium diet (Hill's Prescription Diet z/d; sodium content, 79 mg/100 kcal).

Urinary angiotensinogen intergroup comparisons

Urinary angiotensinogen, indexed with urinary total protein or creatinine, was significantly higher for cats in the CKD group; this did not appear to be driven by amlodipine administration in hypertensive cats **(Figure 1)**. Neither of the indexed urinary angiotensinogen differed significantly between CKD cats that were or were not administered amlodipine **(Supplementary Figure S2)**. In our samples consisting exclusively of neutered cats, sex was also not a dominant factor for indexed urinary angiotensinogen **(Supplementary Figures S3 and S4)**.

Based on receiver operating characteristic curves, indexed angiotensinogen was a better discriminator between groups than UPC. Areas under the curve for urinary angiotensinogen-to-protein ratio, urinary angiotensinogen-to-creatinine ratio, and UPC were 0.827, 0.740, and 0.574, respectively **(Figure 2)**. At the optimal cutoff determined by Youden index maximization, the urinary angiotensinogen-to-protein ratio had a sensitivity of 92.9% and specificity of 64.3%, and the urinary angiotensinogen-to-creatinine

Table 2—Spearman correlation analysis between indexed baseline urinary angiotensinogen concentration or UPC and systolic blood pressure, serum creatinine concentration, or UPC.

	ρ	*P* value
Urinary angiotensinogen-to-protein ratio, control group		
Systolic blood pressure	0.442	.113
Serum creatinine	−0.479	.083
UPC	0.065	.826
Urinary angiotensinogen-to-creatinine ratio, control group		
Systolic blood pressure	0.455	.102
Serum creatinine	−0.497	.070
UPC	0.299	.299
Urine protein-to-creatinine ratio, control group		
Systolic blood pressure	0.169	.565
Serum creatinine	−0.347	.224
Urinary angiotensinogen-to-protein ratio, CKD group		
Systolic blood pressure	0.042	.887
Serum creatinine	0.573	.032*
UPC	0.272	.347
Urinary angiotensinogen-to-creatinine ratio, CKD group		
Systolic blood pressure	0.231	.427
Serum creatinine	0.642	.013*
UPC	0.541	.046*
UPC, CKD group		
Systolic blood pressure	0.417	.138
Serum creatinine	0.270	.350

Samples were collected from 14 purpose-bred cats with surgically induced CKD and 14 community-owned sex- and life stage–matched healthy cats.

*$P < .05$.

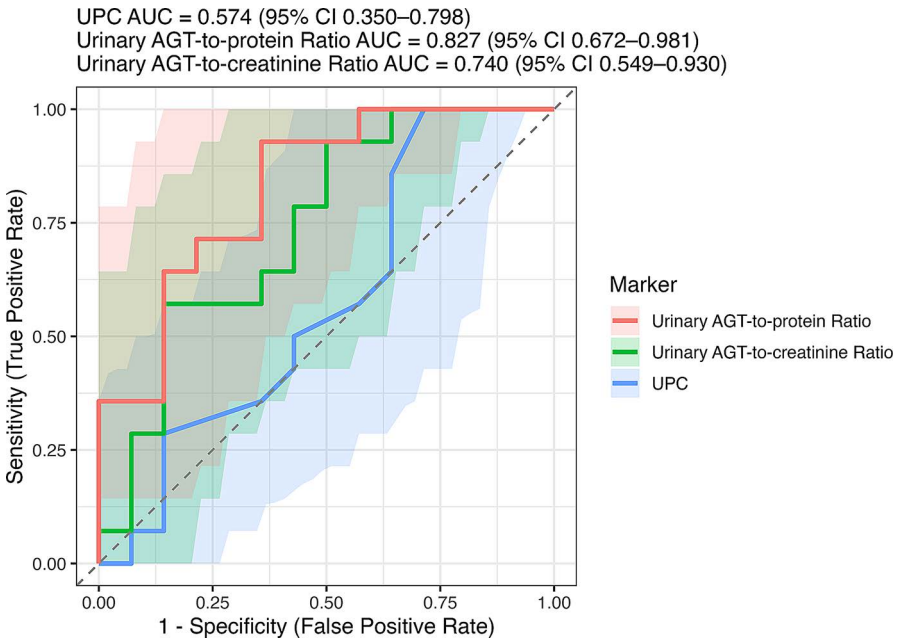


Figure 2—Receiver operating characteristic curves for indexed urinary AGT or urine protein-to-creatinine ratio (UPC) to distinguish cats with surgically induced CKD versus sex- and life stage–matched healthy cats. AUC = Area under curve.

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

ratio had a sensitivity of 92.9% and specificity of 50% for diagnosing CKD.

Correlations between urinary angiotensinogen and clinical variables

Correlations between indexed urinary angiotensinogen or UPC and selected clinical variables at baseline are shown in **Table 2**. In the CKD group, indexed urinary angiotensinogen was positively correlated with serum creatinine concentration (urinary angiotensinogen-to-protein ratio, ρ = 0.573, *P* = .032; urinary angiotensinogen-to-creatinine ratio, ρ = 0.642, *P* = .013).

Correlations between urinary angiotensinogen and circulating RAAS

Correlations between circulating RAAS markers and indexed urinary angiotensinogen are summarized in **Table 3**. In healthy cats (control group), but not cats with CKD, the urinary angiotensinogen-to-creatinine ratio was negatively correlated with multiple circulating RAAS markers (angiotensin II, ρ = −0.547, *P* = .043; angiotensin 1-7, ρ = −0.631, *P* = .016; PRA-S, ρ = −0.600, *P* = .023). However, the same 3 markers were also negatively correlated with UPC, and the urinary angiotensinogen-to-protein ratio was not significantly correlated with any of the selected circulating RAAS markers.

Table 3—Spearman correlation analysis between indexed urinary angiotensinogen and circulating renin-angiotensin-aldosterone system (RAAS) markers in 14 purpose-bred cats with surgically induced CKD and 14 community-owned sex- and life stage–matched healthy cats.

	ρ	*P* value
Urinary angiotensinogen-to-protein ratio, control group		
Serum angiotensin II	−0.323	.260
Serum angiotensin 1-7	−0.477	.085
Serum aldosterone	−0.055	.852
Serum PRA-S	−0.367	.197
Serum ACE-S	0.213	.464
Urinary angiotensinogen-to-creatinine ratio, control group		
Serum angiotensin II	−0.547	.043*
Serum angiotensin 1-7	−0.631	.016*
Serum aldosterone	−0.178	.543
Serum PRA-S	−0.600	.023*
Serum ACE-S	0.235	.418
UPC, control group		
Serum angiotensin II	−0.591	.026*
Serum angiotensin 1-7	−0.560	.037*
Serum aldosterone	−0.136	.643
Serum PRA-S	−0.642	.013*
Serum ACE-S	0.169	.562
Urinary angiotensinogen-to-protein ratio, CKD group		
Serum angiotensin II	−0.235	.418
Serum angiotensin 1-7	−0.121	.681
Serum aldosterone	−0.138	.637
Serum PRA-S	−0.204	.483
Serum ACE-S	−0.015	.958
Urinary angiotensinogen-to-creatinine ratio, CKD group		
Serum angiotensin II	−0.059	.840
Serum angiotensin 1-7	0.011	.970
Serum aldosterone	−0.037	.899
Serum PRA-S	−0.020	.946
Serum ACE-S	−0.218	.455
UPC, CKD group		
Serum angiotensin II	0.130	.657
Serum angiotensin 1-7	0.117	.690
Serum aldosterone	−0.117	.690
Serum PRA-S	0.148	.613
Serum ACE-S	−0.369	.194

*$P < .05$.

ACE-S = Surrogate for angiotensin-converting enzyme activity. PRA-S = Surrogate for plasma renin activity.

Discussion

In this study, urinary angiotensinogen indexed to creatinine or total protein was higher in cats with surgically induced CKD compared to sex- and life stage–matched healthy cats. Additionally, urinary angiotensinogen correlated positively with serum creatinine concentration in cats with surgically induced CKD. This supports its possible role as a biomarker of intrarenal RAS activity and kidney disease as in rodents and human beings.[7]

A major argument for the use of urinary angiotensinogen as a marker of intrarenal RAS activity is that the majority of angiotensinogen found in urine originates from protein expression in kidney tissue as opposed to it being filtered from plasma by the glomerulus.[7] Increased protein expression of angiotensinogen in the kidneys of cats with CKD is supported by previous studies[24,25] showing higher mRNA levels of its gene (ie, *angiotensinogen*). If this is the case, the proportion of angiotensinogen among all urinary protein should increase, whereas if increased angiotensinogen is a mere result of increased overall/indiscriminate urinary protein loss, the proportion of angiotensinogen/total urinary protein should be relatively stable. Therefore, we corrected the urinary angiotensinogen concentration not only relative to urinary creatinine (to account for overall urine concentration) but also relative to urinary total protein. We showed that the proportion of angiotensinogen among all urinary proteins (ie, urinary angiotensinogen-to-protein ratio) is increased in cats with surgically induced CKD relative to healthy cats. Together with the previous findings of elevated *angiotensinogen* mRNA levels in kidneys from cats with CKD,[24,25] these data support that a meaningful proportion of urinary angiotensinogen in cats results from intrarenal expression.

L-type calcium channel blockers, including amlodipine, activate the circulating RAAS in dogs, human beings, and cats.[27,34–39] In this study, amlodipine was not associated with higher urinary angiotensinogen, suggesting it might not activate intrarenal RAS as it does in the circulation. Gender and age also did not appear to be major determinants of urinary angiotensinogen in our study cohort. This is consistent with previous studies[14,40,41] in human beings, which found no significant associations between urinary angiotensinogen and gender or age.

There was a negative correlation between urinary angiotensinogen-to-creatinine ratio and multiple circulating RAAS markers (ie, serum equilibrium concentration of angiotensin II and angiotensin 1-7

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

and PRA-S) in healthy cats. This appeared to be partially driven by a negative correlation between these markers and total urinary protein loss (as represented by UPC); urinary angiotensinogen-to-protein ratio trended toward being negatively correlated with these circulating RAAS markers, but this did not reach statistical significance.

In humans, studies evaluating the associations between circulating RAAS and intrarenal RAS have yielded mixed results. One study[42] focusing on pediatric IgA nephropathy found a negative correlation between urinary aldosterone-to-creatinine ratio, an indicator of circulating RAAS, and urinary angiotensinogen-to-creatinine ratio. Another study[43] in healthy humans found largely no associations between circulating and intrarenal RAS markers except that in healthy adult men there was a negative correlation between plasma angiotensin-converting enzyme concentration and urinary prorenin-to-creatinine ratio. A previous study[24] evaluating cats with CKD induced by ischemia reperfusion found a lack of association between most of the circulating RAAS and kidney transcription of RAS-related genes. Overall, the association between circulating RAAS and intrarenal RAS appears to be complex, likely depending on the population sampled, the marker used, and specific underlying disease.

One notable element in our study is the difference in sodium intake between the CKD and control groups. Diet is known to affect the circulating RAAS, with a low-sodium diet leading to circulating RAAS activation.[44] However, in humans and rodents, an opposite relation has been documented between dietary sodium intake and intrarenal RAS. Rodents receiving a low-sodium diet experienced an activation in circulating but not intrarenal RA(A)S[45]; meanwhile, a high-sodium diet induced a significant increase in intrarenal expression of RAS-related genes and proteins, including mRNA expression of angiotensinogen, and protein/peptide expression of cortext renin and angiotensin II.[46] In a crossover clinical trial in humans (n = 100), a low-sodium diet led to a significant decrease in urinary angiotensinogen, whereas a high-sodium diet showed an opposite effect (ie, a significant increase in urinary angiotensinogen).[47] Altogether, these studies suggest a positive relationship between dietary sodium intake and intrarenal RAS activity. Compared to the control group, the CKD group in our study had a lower dietary sodium intake; however, their urinary angiotensinogen was still higher. This might be due to CKD playing a more dominant factor than dietary sodium intake in determining intrarenal RAS activity in these cats. However, future studies focusing on the effects of diet on intrarenal RAS in cats are needed to clarify this.

This study has several limitations. First, despite similarities in histology, biochemical variables, and clinical presentation,[28] it is unknown whether the intrarenal RAS status in cats with induced CKD via a remnant kidney model is comparable to that in cats with naturally occurring CKD. Second, kidney tissue was not available for this study. Therefore, we cannot verify whether the urinary angiotensinogen is associated with kidney mRNA or protein expression levels or angiotensin II immunostaining in these cats as described in people and rodents.[11–16] The study also had a relatively small sample size; therefore, type II error is possible in the instances where no correlations were found. Finally, cats in the CKD group had a significantly higher SBP than healthy cats. While this is consistent with the common clinical picture, this study could not disentangle the effects of systemic arterial hypertension or its treatment from those of CKD.

In conclusion, we demonstrated that urinary angiotensinogen—a widely recognized intrarenal RAS biomarker in human beings and rodents[11–13,17–19,48,49]—is elevated in cats with surgically induced CKD and correlates positively with serum creatinine in this population. This suggests activation of intrarenal RAS during CKD in cats. Because circulating RAAS activation (based on serum angiotensin peptide concentrations) was not apparent in these cats with induced CKD,[27] these results also highlight that concurrent evaluation of the intrarenal RAS is required for a more complete assessment of this system in health and disease states. Meanwhile, associations between intrarenal and circulating RA(A)S in cats with or without CKD warrant further investigation.

Acknowledgments

None reported.

Disclosures

Drs. Lourenço and Schmiedt have previously received research funding from Ceva Animal Health and Boehringer Ingelheim Vetmedica GmbH. That funding was not related to the present study.

No AI-assisted technologies were used in the composition of this manuscript.

Publisher's Note

The American Veterinary Medical Association (AVMA), the Editor, and the Editorial Board are not responsible for the content, claims, opinions, or conclusions published in the Journal. These are solely those of the author(s), and publication does not imply endorsement by the AVMA, the Editor, or the Editorial Board. The Journal's content is provided for educational purposes only.

Funding

The authors have nothing to disclose.

ORCID

Jane H. C. Huang https://orcid.org/0009-0001-4528-9245

Bianca N. Lourenço https://orcid.org/0000-0001-5249-4645

References

1. Brown CA, Elliott J, Schmiedt CW, Brown SA. Chronic kidney disease in aged cats: clinical features, morphology, and proposed pathogeneses. *Vet Pathol.* 2016;53(2):309–326. doi:10.1177/0300985815622975
2. Conroy M, Brodbelt DC, O'Neill D, Chang YM, Elliott J. Chronic kidney disease in cats attending primary care practice in the UK: a VetCompass study. *Vet Rec.* 2019;184(17):526. doi:10.1136/vr.105100
3. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet.* 2021;398(10302):786–802. doi:10.1016/s0140-6736(21)00519-5

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

4. Rüster C, Wolf G. Angiotensin II as a morphogenic cytokine stimulating renal fibrogenesis. *J Am Soc Nephrol.* 2011;22(7):1189–1199. doi:10.1681/asn.2010040384
5. Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci.* 2008;29(7):367–374. doi:10.1016/j.tips.2008.05.003
6. Wu C-H, Mohammadmoradi S, Chen JZ, Sawada H, Daugherty A, Lu HS. Renin-angiotensin system and cardiovascular functions. *Arterioscler Thromb Vasc Biol.* 2018;38(7):e108–e116. doi:10.1161/ATVBAHA.118.311282
7. Nishiyama A, Kobori H. Independent regulation of renin-angiotensin-aldosterone system in the kidney. *Clin Exp Nephrol.* 2018;22(6):1231–1239. doi:10.1007/s10157-018-1567-1
8. Lin H, Geurts F, Hassler L, et al. Kidney angiotensin in cardiovascular disease: formation and drug targeting. *Pharmacol Rev.* 2022;74(3):462–505. doi:10.1124/pharmrev.120.000236
9. Navar LG, Kobori H, Prieto MC, Gonzalez-Villalobos RA. Intratubular renin-angiotensin system in hypertension. *Hypertension.* 2011;57(3):355–362. doi:10.1161/HYPERTENSIONAHA.110.163519
10. Urushihara M, Kobori H. Intrarenal renin-angiotensin system activation in end-stage renal disease. *Hypertens Res.* 2017;40(4):351–352. doi:10.1038/hr.2017.7
11. Wu L, Yang M, Feng X, et al. Urinary angiotensinogen: an indicator of active antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Nephrol Dial Transplant.* 2018;34(5):838–847. doi:10.1093/ndt/gfy112
12. Yamamoto T, Nakagawa T, Suzuki H, et al. Urinary angiotensinogen as a marker of intrarenal angiotensin II activity associated with deterioration of renal function in patients with chronic kidney disease. *J Am Soc Nephrol.* 2007;18(5):1558–1565. doi:10.1681/asn.2006060554
13. Zhang XY, Ding XQ, Lv WL, Teng J, Zhong YH. ELISA examining urinary angiotensinogen as a potential indicator of intrarenal renin-angiotensin system (RAS) activity: a clinical study of 128 chronic kidney disease patients. *Mol Biol Rep.* 2013;40(10):5817–5824. doi:10.1007/s11033-013-2687-z
14. Nishiyama A, Konishi Y, Ohashi N, et al. Urinary angiotensinogen reflects the activity of intrarenal renin-angiotensin system in patients with IgA nephropathy. *Nephrol Dial Transplant.* 2011;26(1):170–177. doi:10.1093/ndt/gfq371
15. Urushihara M, Nagai T, Kinoshita Y, et al. Changes in urinary angiotensinogen posttreatment in pediatric IgA nephropathy patients. *Pediatr Nephrol.* 2015;30(6):975–982. doi:10.1007/s00467-014-3028-8
16. Cao W, Jin L, Zhou Z, et al. Overexpression of intrarenal renin-angiotensin system in human acute tubular necrosis. *Kidney Blood Press Res.* 2016;41(6):746–756. doi:10.1159/000450564
17. Juretzko A, Steinbach A, Hannemann A, et al. Urinary angiotensinogen and renin excretion are associated with chronic kidney disease. *Kidney Blood Press Res.* 2017;42(1):145–155. doi:10.1159/000474932
18. Mills KT, Kobori H, Hamm LL, et al. Increased urinary excretion of angiotensinogen is associated with risk of chronic kidney disease. *Nephrol Dial Transplant.* 2012;27(8):3176–3181. doi:10.1093/ndt/gfs011
19. Jang HR, Kim SM, Lee YJ, et al. The origin and the clinical significance of urinary angiotensinogen in proteinuric IgA nephropathy patients. *Ann Med.* 2012;44(5):448–457. doi:10.3109/07853890.2011.558518
20. van den Heuvel M, Batenburg WW, Jainandunsing S, et al. Urinary renin, but not angiotensinogen or aldosterone, reflects the renal renin-angiotensin-aldosterone system activity and the efficacy of renin-angiotensin-aldosterone system blockade in the kidney. *J Hypertens.* 2011;29(11):2147–2155. doi:10.1097/HJH.0b013e32834bbcbf
21. Roksnoer LCW, Verdonk K, van den Meiracker AH, Hoorn EJ, Zietse R, Danser AHJ. Urinary markers of intrarenal renin-angiotensin system activity in vivo. *Curr Hypertens Rep.* 2013;15(2):81–88. doi:10.1007/s11906-012-0326-z
22. Mitani S, Yabuki A, Taniguchi K, Yamato O. Association between the intrarenal renin-angiotensin system and renal injury in chronic kidney disease of dogs and cats. *J Vet Med Sci.* 2013;75(2):127–133. doi:10.1292/jvms.12-0314
23. Taugner F, Baatz G, Nobiling R. The renin-angiotensin system in cats with chronic renal failure. *J Comp Pathol.* 1996;115(3):239–252. doi:10.1016/s0021-9975(96)80082-x
24. Huang JHC, Lourenço BN, Schmiedt CW, Tarigo JL, Coleman AE. Post hoc comparison of the intrarenal and circulating renin-angiotensin(-aldosterone) systems in cats with ischemia-induced chronic kidney disease. *Physiol Rep.* 2025;13(12):e70417. doi:10.14814/phy2.70417
25. Lourenço BN, Coleman AE, Berghaus RD, Tarigo JL, Schmiedt CW, Brown SA. Characterization of the intrarenal renin-angiotensin system in cats with naturally occurring chronic kidney disease. *J Vet Intern Med.* 2022;36(2):647–655. doi:10.1111/jvim.16361
26. Huang JHC, Lourenço BN, Coleman AE, Berghaus LJ, Whitfield-Cargile C. Development and validation of a sandwich ELISA for measurement of angiotensinogen in feline urine. *Am J Vet Res.* 2026:1–7. doi:10.2460/ajvr.26.04.0172
27. Huang JH, Lourenço BN, Schmiedt CW, Coleman AE. Classical and alternative renin-angiotensin-aldosterone systems in a feline remnant kidney model. *Am J Vet Res.* 2025;86(11):ajvr.25.06.0201 doi:10.2460/ajvr.25.06.0201
28. Schmiedt CW, Beita KG, Lourenço BN, et al. A remnant kidney surgery model in cats induces acute and chronic outcomes that mimic spontaneous chronic kidney disease. *Am J Vet Res.* 2023;84(8):ajvr.23.04.0081. doi:10.2460/ajvr.23.04.0081
29. R: a language and environment for statistical computing. R Foundation for Statistical Computing. Version 4.4.1. Accessed June 14, 2026. https://www.R-project.org/
30. Guo Z, Poglitsch M, Cowley D, et al. Effects of ramipril on the aldosterone/renin ratio and the aldosterone/angiotensin II ratio in patients with primary aldosteronism. *Hypertension.* 2020;76(2):488–496. doi:10.1161/hypertensionaha.120.14871
31. Pavo N, Goliasch G, Wurm R, et al. Low- and high-renin heart failure phenotypes with clinical implications. *Clin Chem.* 2018;64(3):597–608. doi:10.1373/clinchem.2017.278705
32. Quimby J, Gowland S, Carney H, DePorter T, Plummer P, Westropp J. 2021 AAHA/AAFP feline life stage guidelines. *J Feline Med Surg.* 2021;23(3):211–233. doi:10.1177/1098612X21993657
33. IRIS guidelines 2023. International Renal Interest Society. Accessed March 19, 2026. https://www.iris-kidney.com/iris-guidelines-1
34. Jepson RE, Syme HM, Elliott J. Plasma renin activity and aldosterone concentrations in hypertensive cats with and without azotemia and in response to treatment with amlodipine besylate. *J Vet Intern Med.* 2014;28(1):144–153. doi:10.1111/jvim.12240
35. Atkins CE, Rausch WP, Gardner SY, Defrancesco TC, Keene BW, Levine JF. The effect of amlodipine and the combination of amlodipine and enalapril on the renin-angiotensin-aldosterone system in the dog. *J Vet Pharmacol Ther.* 2007;30(5):394–400. doi:10.1111/j.1365-2885.2007.00894.x
36. Vischer AS, Kuster GM, Twerenbold R, et al. Influence of antihypertensive treatment on RAAS peptides in newly diagnosed hypertensive patients. *Cells.* 2021;10(3):534. doi:10.3390/cells10030534
37. Ward JL, Guillot E, Domenig O, Ware WA, Yuan L, Mochel JP. Circulating renin-angiotensin-aldosterone system activity in cats with systemic hypertension or cardiomyopathy. *J Vet Intern Med.* 2022;36(3):897–909. doi:10.1111/jvim.16401

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/

38. Lourenço BN, Huang JH, Reno L, Toborowsky C, Coleman AE. Circulating renin-angiotensin-aldosterone system markers in cats with non-hypertensive chronic kidney disease or systemic arterial hypertension. *J Vet Intern Med.* 2026;40(3):aalag079. doi:10.1093/jvimsj/aalag079
39. Adin D, Atkins C, Domenig O, Glahn C, DeFrancesco T, Meurs K. Evaluation of renin-angiotensin-aldosterone system components and enzymes in systemically hypertensive cats receiving amlodipine. *Animals.* 2023;13(22):3479. doi:10.3390/ani13223479
40. Kobori H, Alper AB, Shenava R, et al. Urinary angiotensinogen as a novel biomarker of the intrarenal renin-angiotensin system status in hypertensive patients. *Hypertension.* 2009;53(2):344–350. doi:10.1161/HYPERTENSIONAHA.108.123802
41. Kobori H, Urushihara M, Xu JH, Berenson GS, Navar LG. Urinary angiotensinogen is correlated with blood pressure in men (Bogalusa Heart Study). *Hypertens.* 2010;28(7):1422–1428. doi:10.1097/HJH.0b013e3283392673
42. Chetwynd AJ, Marro J, Northey SJ, Hughes DJ, Oni L. Variations in urinary renin-angiotensin-aldosterone component concentrations in paediatric IgA vasculitis nephritis. *Int J Transl Med.* 2022;2(4):597–606. doi:10.3390/ijtm2040045
43. Pringle KG, Sykes SD, Lumbers ER. Circulating and intrarenal renin-angiotensin systems in healthy men and nonpregnant women. *Physiol Rep.* 2015;3(10):e12586. doi:10.14814/phy2.12586
44. Yu S, Morris JG. Sodium requirement of adult cats for maintenance based on plasma aldosterone concentration. *J Nutr.* 1999;129(2):419–423. doi:10.1093/jn/129.2.419
45. Shao W, Seth DM, Prieto MC, Kobori H, Navar LG. Activation of the renin-angiotensin system by a low-salt diet does not augment intratubular angiotensinogen and angiotensin II in rats. *Am J Physiol Renal Physiol.* 2013;304(5):F505–F514. doi:10.1152/ajprenal.00587.2012
46. Wu H, Liang Y, Zheng Y, et al. Up-regulation of intrarenal renin-agiotensin system contributes to renal damage in high-salt induced hypertension rats. *Kidney Blood Press Res.* 2014;39(6):526–535. doi:10.1159/000368463
47. Rebholz CM, Chen J, Zhao Qi, et al. Urine angiotensinogen and salt-sensitivity and potassium-sensitivity of blood pressure. *J Hypertens*. 2015;33(7):1394–1400.
48. Dou Y, Song D, Wang C, et al. The role of urinary angiotensinogen in kidney interstitial inflammation and renal prognosis. *Iran J Kidney Dis.* 2019;13(6):372–379.
49. Park CH, Kim HW, Park JT, et al. Intrarenal renin-angiotensin system activation alters relationship between systolic blood pressure and progression of chronic kidney disease. *Hypertension.* 2023;80(5):1024–1034. doi:10.1161/hypertensionaha.122.20824

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.

Downloaded from https://avmajournals.avma.org at 2026-11-11 via Open Access. This is an open access article distributed under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/). http://creativecommons.org/licenses/by-nc/4.0/