Received: 10 January 2023 | Accepted: 23 August 2023

DOI: 10.1111/jvim.16849

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Urine concentrating ability in cats with hyperthyroidism: Influence of radioiodine treatment, masked azotemia, and iatrogenic hypothyroidism

Mark E. Peterson [1,2] | Mark Rishniw [2,3]

[1]Animal Endocrine Clinic, 21 West 100th Street, New York, New York, USA

[2]College of Veterinary Medicine, Cornell University, Ithaca, New York, USA

[3]Veterinary Information Network, Davis, California, USA

Correspondence
Mark E. Peterson, Animal Endocrine Clinic, 220 Manhattan Avenue, New York, NY, USA.
Email: drpeterson@animalendocrine.com

Abstract

Background: Hyperthyroid cats often have urine specific gravity (USG) values <1.035. It remains unclear how USG changes after treatment, if USG can be used to predict azotemia after treatment, or how iatrogenic hypothyroidism influences USG values.

Objectives: To determine the proportion of hyperthyroid cats with USG <1.035 vs ≥1.035; if USG changes after treatment; and whether USG <1.035 correlated with unmasking of azotemia or hypothyroidism.

Animals: Six hundred fifty-five hyperthyroid cats treated with radioiodine; 190 clinically normal cats.

Methods: Prospective, before-and-after study. Hyperthyroid cats had serum thyroxine, thyroid-stimulating hormone, and creatinine concentrations, and USG measured before and 6 months after successful treatment with radioiodine.

Results: Of untreated hyperthyroid cats, USG was ≥1.035 in 346 (52.8%) and <1.035 in 309 (47.2%). After treatment, 279/346 (80.6%) maintained USG ≥1.035, whereas 67/346 (19.4%) became <1.035; 272/309 (88%) maintained USG <1.035, whereas 37/309 (12%) became ≥1.035. Only 22/346 (6.4%) with USG ≥1.035 developed azotemia after treatment, compared with 136/309 (44%) with <1.035 ($P < .001$). Of cats remaining nonazotemic, 38% had USG <1.035, compared with 20% of normal cats ($P < .001$). The 137 cats with iatrogenic hypothyroidism had lower USG after treatment than did 508 euthyroid cats (1.024 vs 1.035), but USGs did not change after levothyroxine supplementation. USG <1.035 had high sensitivity (86.1%) but moderate specificity (65.2%) in predicting azotemia after treatment.

Conclusions and Clinical Importance: Hyperthyroidism appears not to affect USG in cats. However, cats with evidence of sub-optimal concentrating ability before radioiodine treatment (USG < 1.035) are more likely to develop azotemia and unmask previously occult chronic kidney disease. Iatrogenic hypothyroidism itself did not appear to affect USG values.

Abbreviations: ^{131}I, radioiodine; CI, confidence interval; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone; USG, urine specific gravity.

KEYWORDS
^{131}I, CKD, feline, hypothyroidism, kidney, radioactive iodine, thyroid gland, urine specific gravity

1 | INTRODUCTION

Hyperthyroid cats commonly have sub-maximally concentrated urine, with urine specific gravity (USG) <1.035.[1-3] This is of clinical importance, since hyperthyroidism is a reported risk factor for chronic kidney disease (CKD),[4-6] in which a USG <1.035 is expected.[7,8] Furthermore, hyperthyroidism can complicate (mask) the diagnosis of azotemic CKD by increasing renal blood flow and glomerular filtration rate (GFR)[9-12] and decreasing body muscle mass,[13,14] thereby lowering serum creatinine concentration to within its reference interval. Consequently, many hyperthyroid cats with concurrent CKD only develop azotemia after successful treatment, when hyperthyroidism no longer maintains high renal blood flow and GFR.[9,12,15-18] Therefore, one might expect that the detection of USG <1.035 could help predict which untreated hyperthyroid cats have concurrent (but masked) azotemic CKD, a finding which has been reported in some,[2,10] but not in other[1,15,17] studies.

If and how USG concentrating ability changes after treatment of cats with hyperthyroidism and how these changes in USG are related to azotemia remains unclear. Small case series of treated hyperthyroid cats suggest that the USG either remains unchanged[10,18] or decreases after successful treatment.[15-17] Only rarely does USG increase after treatment, counter to the hypothesis that hyperthyroidism itself causes the suboptimal urine concentration. This suggests that factors other than hyperthyroidism might be responsible for "less-than-maximally concentrated" USG values (<1.035).

Complicating this situation is the common development of iatrogenic hypothyroidism, which can produce azotemia by decreasing GFR and renal blood flow to subnormal levels.[4,19-23] Such azotemia would be expected to improve once thyroid hormone replacement therapy normalizes GFR and renal blood flow.[23-25] In addition, hypothyroidism has been reported to impair urine concentrating ability in some,[26,27] but not all,[28] studies of human patients, an effect that can sometimes be reversed with thyroid hormone treatment.[26,27] To our knowledge, no reports on urine concentration in hypothyroid cats, either with or without azotemia, exist.

In this study, we sought to determine the prevalence of concentrated (≥1.035) vs sub-maximally concentrated (<1.035) USG in a large cohort of nonazotemic hyperthyroid cats. Furthermore, we examined if and how urine concentrating ability changes in these cats after successful radioiodine (^{131}I) treatment; examined if any differences in pretreatment USG exist in treated cats that remain nonazotemic vs become azotemic, if any differences in USG exist in ^{131}I-treated cats that remain nonazotemic vs age-matched clinically normal cats, and if any differences in USG exist in ^{131}I-treated cats that become euthyroid vs hypothyroid. Finally, we examined whether pretreatment USG <1.035 could predict development of azotemia in hyperthyroid cats after successful ^{131}I treatment and to determine if iatrogenic hypothyroidism influenced the ability of USG to predict development of azotemia after treatment.

2 | MATERIALS AND METHODS

2.1 | Study design and selection of animals

2.1.1 | Hyperthyroid cats

All hyperthyroid cats referred to the Animal Endocrine Clinic for treatment with ^{131}I over the 5-year period from January 2017 to January 2022 were evaluated for eligibility into this prospective, before-and-after study.[29,30] To be eligible for inclusion, untreated hyperthyroid cats underwent an evaluation that included review of medical records, physical examination, laboratory testing (complete blood count, serum biochemical profile, and complete urinalysis, including determination of USG), determination of serum thyroid hormones (total T_4, T_3, and TSH),[31-33] and qualitative and quantitative thyroid scintigraphy.[34,35] In cats treated with methimazole, owners discontinued the drug 1-2 weeks before evaluation.[34,35] Owners feeding a low-iodine diet (Hill's Prescription Diet y/d Feline, Topeka, Kansas, USA) were instructed to feed an iodine-replete diet for at least 4 weeks before treatment. In all cats, the administered ^{131}I dose was calculated based on a previously described dosing algorithm.[36-38]

We excluded hyperthyroid cats with pre-existent azotemia (defined as serum creatinine >2.0 mg/dL), as well as those in which cystocentesis was not possible, either because of small bladder size or fractious nature of the cat. We also excluded cats whose owners did not wish to return for follow-up evaluation or were lost to follow-up, as well as cats that remained hyperthyroid after ^{131}I treatment (Figure 1).

All hyperthyroid cats were reevaluated approximately 6 months after ^{131}I treatment. At recheck ^{131}I, all cats underwent an evaluation that included medical history review and physical examination. All cats again had urine collected for determination of USG and blood collected for serum biomarkers of renal (ie, creatinine, urea nitrogen, and symmetric dimethylarginine [SDMA] concentrations) and thyroid (T_4, and TSH concentrations) function.

2.1.2 | Clinically normal, euthyroid cats

These cats were recruited at time of routine evaluation and were used as euthyroid controls to establish reference intervals for serum creatinine concentration and USG. Cats had to be ≥7 years old and considered healthy by their owners. None of these cats had any signs of illness, and all were normal on physical examination. These cats also were evaluated by routine laboratory testing (CBC, serum biochemical profile, and complete urinalysis), as well as serum T_4 and TSH concentrations to exclude hyperthyroidism. We excluded cats in which urine could not be collected by cystocentesis.

Almost all of these cats had been enrolled as euthyroid controls in a previous study of subclinical bacteriuria.[3] Ethics approval was

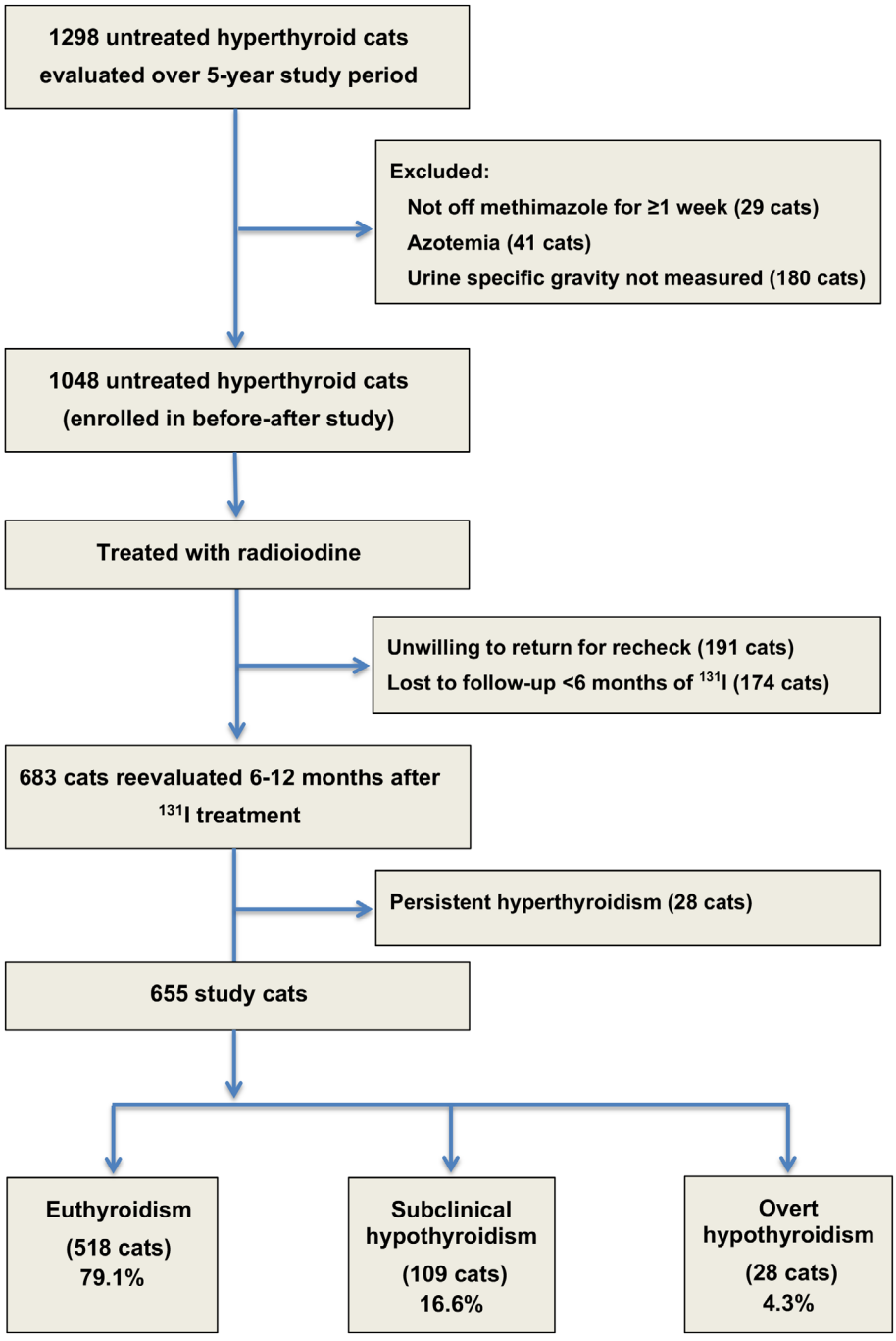

FIGURE 1 Flowchart for enrollment of hyperthyroid cats in the before-after study, separated into 3 thyroid outcome groups.

obtained from the Institution's Animal Care and Use Committee. All owners provided informed consent.

2.2 | Collection and processing of urine samples for USG determination

Cystocentesis was performed without sedation on cats in lateral recumbency with manual palpation of the bladder and alcohol skin preparation. Urine samples for complete urinalysis (≥3 mL) was placed in appropriate sterile, plastic collection tubes, kept at 4°C, and transported to the laboratory (IDEXX Reference Laboratories, Westbrook, Maine, USA) where they were processed and analyzed within 12 hours of collection. USG was measured with a refractometer (Misco Vetmed Refractometer, Solon, Ohio, USA), which was calibrated using distilled water at room temperature at the beginning of each shift. All procedures for routine urinalyses were performed by trained laboratory technicians.

2.3 | Classification of urine concentration

Based on the USG value, we classified each cat's pretreatment and post-treatment urine concentration as concentrated (≥1.035),

moderately concentrated (1.013-1.034), isosthenuric (1.008-1.012), or hyposthenuric (<1.008).[39]

2.4 | Classification of azotemia and thyroid subgroups after ^{131}I treatment

Based on results of follow-up testing after ^{131}I treatment (median time, 6 months), we classified our cats as azotemic or nonazotemic, with renal azotemia defined as a serum creatinine concentration >2.0 mg/dL. All azotemic cats had the diagnosis confirmed by documenting persistent azotemia on 2 or more consecutive occasions (at 1- to 3-month intervals). Cats that developed azotemia after ^{131}I treatment were presumed to have had concurrent, but masked, azotemic kidney disease at the time of diagnosis. All other cats were defined as nonazotemic (serum creatinine ≤ 2.0 mg/dL).

Based on serum concentrations of T_4 and TSH measured after treatment with ^{131}I, we classified the cats' thyroid status into 1 of 3 categories: euthyroid (T_4, 1.0-3.8 μg/dL; TSH ≤ 0.30 ng/mL), overtly hypothyroid (T_4 < 1.0 μg/dL; TSH > 0.30 ng/mL), and subclinically hypothyroid (T_4, 1.0-2.5 μg/dL; TSH > 0.30 ng/mL), as previously described.[25,32,36] Cats that remained persistently hyperthyroid were excluded from study (Figure 1).

2.5 | Data and statistical analyses

Data were assessed for normality by the D'Agostino-Pearson test and by visual inspection of graphical plots.[40] Data were not normally distributed; therefore, all analyses used were performed using nonparametric tests.

We used data from the 190 clinically normal cats to establish reference intervals for serum creatinine concentration and USG by a nonparametric method to identify the central 95th percentile interval (ie, 2.5 through 97.5th percentile range).[41] We also calculated 90% confidence intervals (CIs) for the lower and upper limits of each reference interval.

Results for continuous data (ie, age, serum T_4, TSH, creatinine, and USG) are expressed as median (IQR, 25th-75th percentile) and represented graphically as box-and-whisker plots (Tukey method).[42] Comparisons between 2 continuous variables between groups or within groups (before-after) were analyzed with the Mann-Whitney *U* test and Wilcoxon signed ranks test, respectively. Comparisons between 3 continuous variables (before, after ^{131}I, and again after L-T_4 treatment) were analyzed with the Friedman test. Results for qualitative (categorical) data are expressed as ratio (eg, breed, sex) or percent of cats (eg, prevalence of underweight, methimazole use). Categorical variables were compared between groups by Chi-square or Fisher's exact tests. Finally, we used the Holm-Bonferroni method to account for multiple comparisons by reducing the family-wise error rate (Type 1 errors).[43,44]

We also calculated the sensitivity and specificity for USG <1.035 as a predictor of pre-azotemic (masked) kidney disease after successful ^{131}I therapy.[45,46] We performed these calculations in all 655 treated hyperthyroid cats, as well as separately for euthyroid and iatrogenic hypothyroid cats.

Statistical analyses were performed using proprietary statistical software (GraphPad Prism, version 9.5; GraphPad Software, La Jolla, California, USA; MedCalc, version 20.1, MedCalc Statistical Software, Ltd, Ostend, Belgium).

3 | RESULTS

3.1 | Study cat characteristics

3.1.1 | Cats with hyperthyroidism

Over the 5-year study period, we treated 1048 hyperthyroid cats that were eligible for inclusion and initially enrolled in our study. Of these, 365 cats were not available for recheck were excluded from further study (Figure 1). The remaining 683 cats were reexamined and retested at a median of 6.2 months (IQR, 6-7.4 months; range, 5-12 months) after ^{131}I treatment; 28 cats remained persistently hyperthyroid and were excluded, leaving 655 cats for analysis.

The 655 hyperthyroid cats ranged in age from 5 to 20 years (median, 12.0 years; Table S1). Breeds included domestic longhair and shorthair (580 cats; 88.6%), Siamese (n = 18), Maine Coon (n = 17), Ragdoll (n = 7), Persian (n = 6), Bengal (n = 4), Bombay (n = 3), Manx (n = 3), Norwegian Forest Cat (n = 3), Burmese (n = 2), Russian Blue (n = 2), and Abyssinian, American Curl, American shorthair, Balinese, British shorthair, Chartreux, Havana Brown, Scottish Fold, Siberian, and Tonkinese (1 cat each). Of these, 343 (52.4%) were spayed females and 312 (47.6%) were neutered males (Table S1).

Hyperthyroid cats weighed 1.6 to 9.2 kg (median, 4.4 kg); 210 (32%) cats were underweight, 354 (54%) had an ideal body condition score, and 91 (13.9%) were overweight. Muscle loss was detected in 468 (71.5%) of cats (Table S1).

The time from diagnosis to ^{131}I treatment ranged from 6 days to 5 years (median, 81 days). Three hundred twenty-eight cats (50%) had been treated with methimazole for a median of 60 days, whereas the remaining 327 had never received methimazole (Table S1). In all methimazole-treated cats, the drug was discontinued ≥1 week (median, 7 days; IQR, 7-15 days; range, 7-150 days) before treatment with ^{131}I.

3.1.2 | Clinically normal cats

Of 202 clinically normal cats evaluated as controls, we could not collect urine by cystocentesis in 12 cats, either because of small bladder size or the nature of the cat, leaving 190 apparently healthy cats for analysis.

The clinically normal cats ranged in age from 7 to 19 years (median, 12.0 years; 25-75th percentile, 10-13 years), similar to the age of the hyperthyroid cats ($P = .07$). Breeds included domestic longhair and shorthair (n = 167), Siamese (n = 6), Persian (n = 4), American Shorthair (n = 2), British Shorthair, Burmese, Chartreux, Himalayan, Egyptian

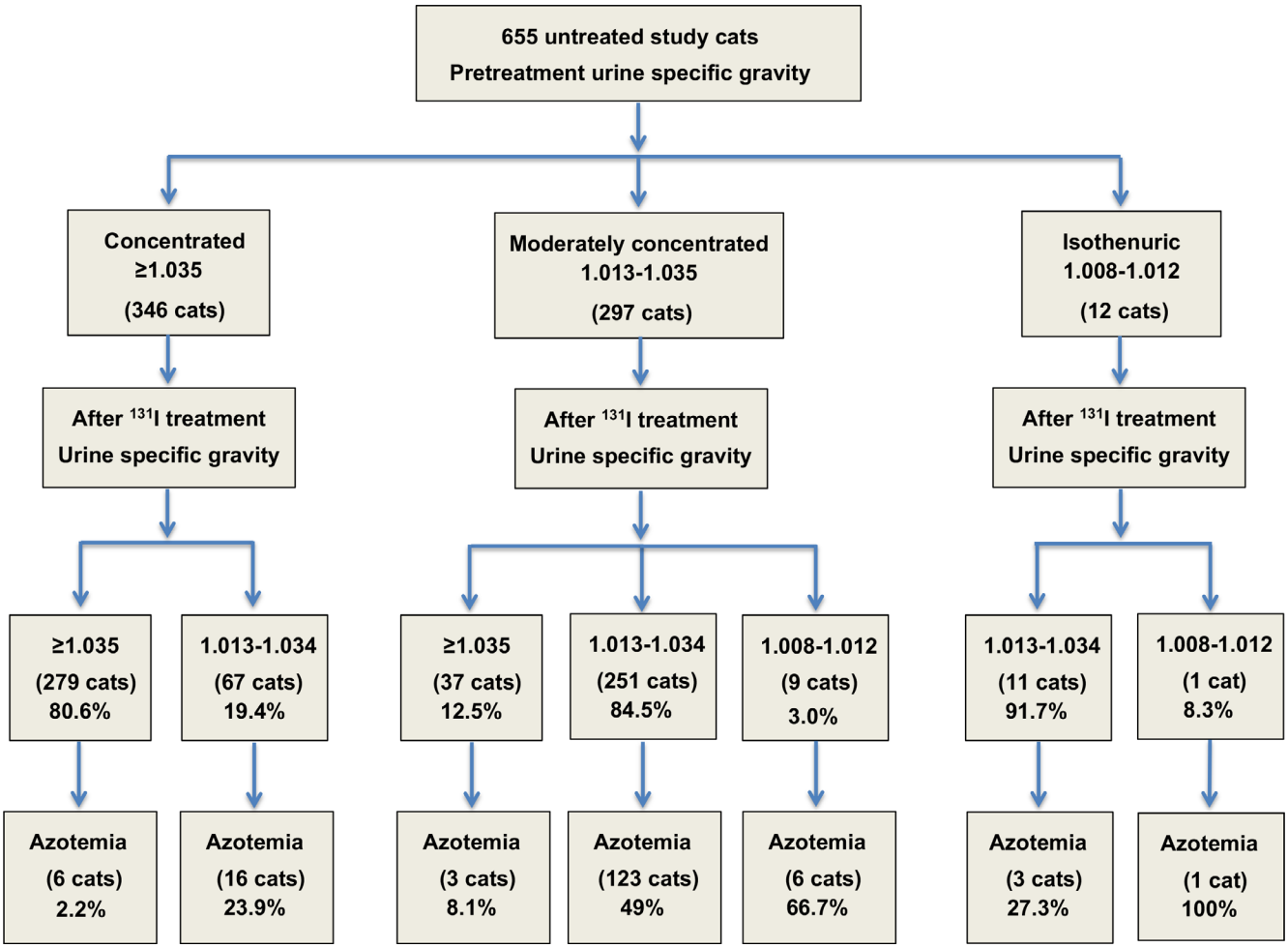

FIGURE 2 Flowchart for categorization of the urine specific gravity values of hyperthyroid cats, before and after treatment, into concentrated, moderately concentrated, and isosthenuric groups, as well as the number of cats that developed azotemia in each subgroup.

Mau, Japanese Bobtail, Maine Coon, Ocicat, Rag doll, and Russian Blue, and Tonkinese (1 cat each). Of these cats, 96 (50.5%) were neutered males and 94 were spayed females. These euthyroid cats did not differ from the hyperthyroid cats in breed ($P = .8$) or sex ($P = .51$) distribution.

The 190 euthyroid cats weighed 2.8 to 9.9 kg (median, 5.0 kg); 4 (2%) of these cats were underweight, 122 (64.2%) had an ideal body condition score, and 64 (33.7%) were overweight. Euthyroid cats were heavier ($P < .001$) than hyperthyroid cats. Similarly, the euthyroid cats were less likely to be underweight and more likely to be overweight, as compared to the hyperthyroid cats ($P < .001$).

The reference intervals for serum creatinine concentrations and USG, calculated from the results in these 190 clinically normal cats, were as follows: serum creatinine concentration = 0.8 mg/dL (90% CI, 0.6-0.9 mg/dL) to 2.0 mg/dL (90% CI, 2.0-2.1 mg/dL); and USG = 1.018 (90% CI, 1.016-1.022) to 1.065 (90% CI, 1.058-1.070). Of these cats, 152 (80%) had USG >1.035, whereas 38 (20%) had USG <1.035. Only 24 (12.6.8%), 16 (8.4%) and 9 (4.7%) cats had USG <1.030, <1.025 and <1.020 respectively (Figure S1).

3.2 | Untreated hyperthyroid cats divided into groups based on UGS ≥1.035 vs USG <1.035

Of the 655 hyperthyroid cats, 346 (52.8%) had pretreatment USG values that were concentrated (≥1.035), 297 (45.4%) cats had USG values that were moderately concentrated (1.013-1.034), and 12 (1.8%) cats had USG values that were isosthenuric (1.008-1.012; Figure 2). No cats had a dilute USG (<1.008). Due to the small numbers of cats with isosthenuria, we combined cats with moderately concentrated and isosthenuric USG values to make a group of 309 cats with USG <1.035 (Figures 3 and 4).

Compared with the 346 cats with concentrated (≥1.035) USG, the 309 cats with pretreatment USG <1.035 were older (13 vs 11 years; $P < .001$) and thinner (4.2 vs 4.5 kg; $P < .002$) (Table S1). None of the other signalment variables differed between the 2 groups.

The 309 cats with pretreatment USG <1.035 had higher pretreatment serum concentrations of creatinine (1.2 vs 0.9 mg/dL; $P < .001$), urea nitrogen (30 vs 24 mg/dL; $P < .001$), and SDMA (12 vs 10 μg/dL; $P < .001$) than the 346 cats with USG ≥1.035 (Table S1; Figure 4B).

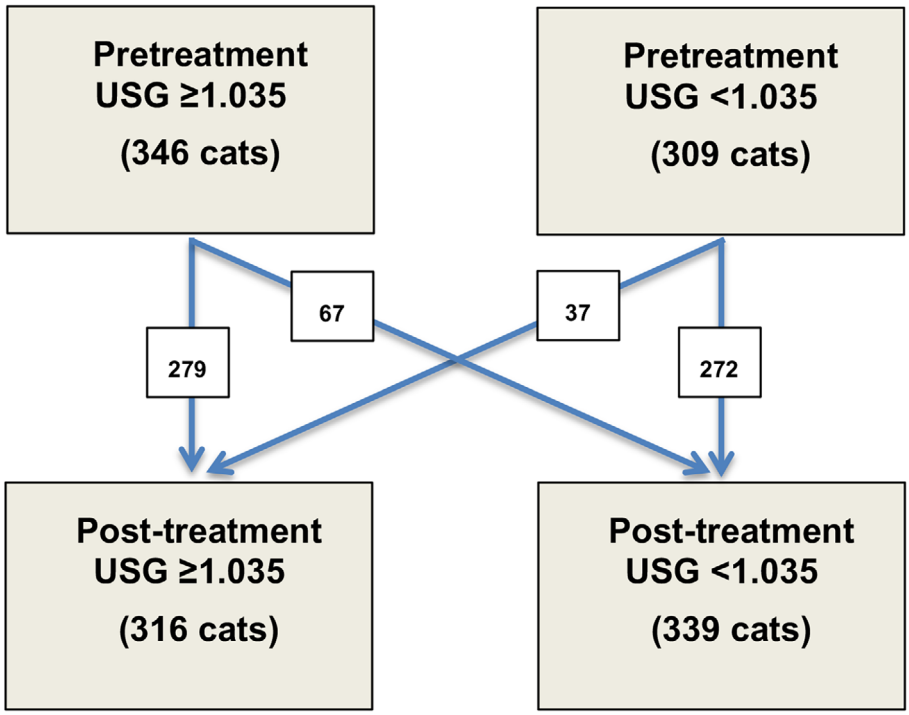

FIGURE 3 Flowchart showing changes in urine specific gravity (USG) values after radioiodine (^{131}I treatment in 346 cats with pretreatment USG ≥1.035 and 309 cats with pretreatment USG <1.035).

Serum concentrations of other chemistry values, including calcium and potassium, did not differ between the 2 groups. Cats in both groups also had similar serum T_4, T_3, and TSH concentrations (Table S1).

The 346 cats with USG ≥1.035 and 309 cats with USG <1.035 had a similar prevalence of bilateral and unilateral thyroid nodules (Table S1). Similarly, cats in both groups had similar values for the thyroid: salivary ratio, ^{131}I dose (severity) score, and calculated ^{131}I dose (Table S1).

3.3 | ^{131}I-treated cats divided into groups based on pretreatment UGS ≥1.035 vs USG <1.035

The 655 ^{131}I-treated hyperthyroid cats were reevaluated at median time of 6.2 months (range, 4.2-12.2 months), with no difference in the time from treatment between cats with pretreatment USG ≥1.035 and <1.035 (6.2 vs 6.0 months; $P = .58$; Table S2).

3.3.1 | Urine specific gravity

After successful treatment with ^{131}I, USG decreased slightly in the 346 cats with USG ≥1.035 ($P < .001$) but did not change ($P = .56$) in the 309 cats with USG <1.035 (Figure 4A). After ^{131}I treatment, the USG in cats with pre-treatment USG ≥1.035 remained much higher ($P < .001$) than the USG in cats with pre-treatment USG <1.035 (Table S2; Figure 4A).

Of the 346 cats that had concentrated USG before treatment, 279 (81%) maintained USG ≥1.035 after treatment, whereas 67 (19%) of these cats developed a USG of 1.013-1.034 (Figures 2 and 3). None of these cats became isosthenuric.

Of the 309 cats that had pre-treatment USG values <1.035, 272 (88%) maintained USG <1.035, whereas 37 (12%) developed a USG ≥1.035 after treatment (Figures 2 and 3). Of these 37 cats that changed from <1.035 to ≥1.035 after treatment, 34 (91.9%) had pre-treatment USG values ≥1.020. Of the 297 cats that had pre-treatment USG of 1.013-1.034, 9 (3%) became isosthenuric after treatment (Figure 2). Of the 12 cats with pre-treatment isosthenuric USG, 11 (91.7%) developed a USG of 1.013-1.034 after treatment and 1 remained isosthenuric (Figure 2).

3.3.2 | Serum creatinine concentrations

Cats with USG <1.035 had higher serum creatinine concentrations before and after treatment than cats with USG ≥1.035 (Tables S1 and S2; $P < .0001$). After treatment, serum creatinine concentrations increased in both groups of cats ($P < .0001$), with 158/655 (24.1%) cats developing azotemia (Figures 2 and 4B). Similarly, serum urea nitrogen and SDMA concentrations increased in both groups of cats after treatment ($P < .001$; Tables S1 and S2). More cats with pretreatment USG <1.035 developed post-treatment azotemia than did cats with USG ≥1.035 (44% vs 6.4%; $P < .001$; Table S2).

3.3.3 | Serum T_4 and TSH concentrations

After treatment, serum T_4 concentrations decreased and serum TSH concentrations increased in the 655 cats (Tables S1 and S2;

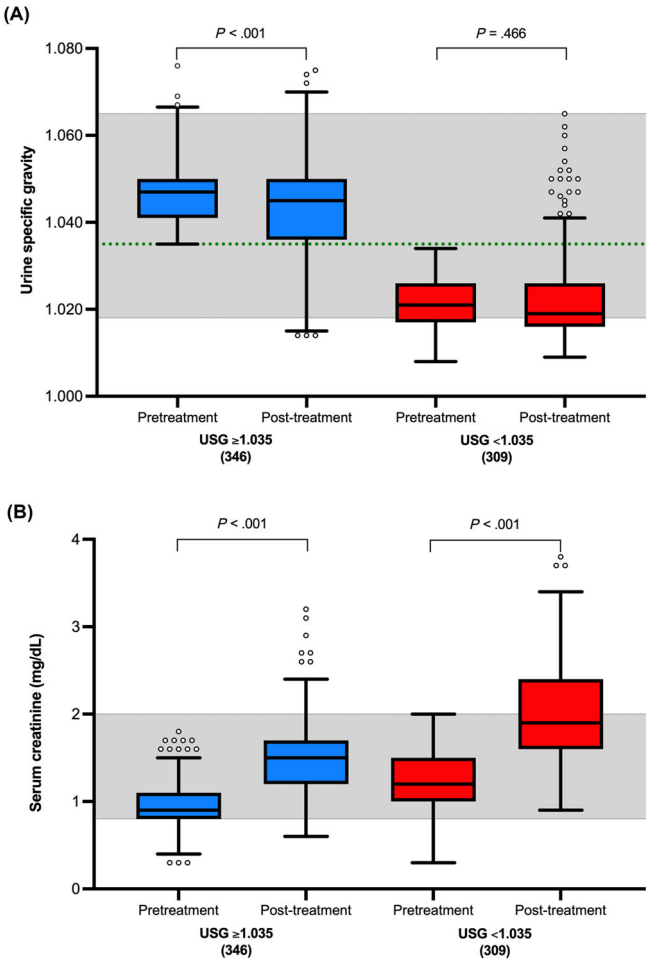

FIGURE 4 Boxplots of urine specific gravity (USG) and serum creatinine concentrations in 655 hyperthyroid cats (before and after ^{131}I treatment), divided into 346 cats with pretreatment USG ≥1.035 and 309 cats with pretreatment USG <1.035. (A) Pre- and post-treatment USG in 346 cats with pretreatment USG ≥1.035 and in 309 cats with pretreatment USG <1.035; (B) Pre- and post-treatment serum creatinine concentrations in 346 cats with pretreatment USG ≥1.035 and in 309 cats with pretreatment USG <1.035. Boxes represent the interquartile range (IQR; 25th to 75th percentile). The horizontal bar in each box represents the median value. The whiskers indicate the range of data values unless outliers are present, in which case the whiskers extend to a maximum of 1.5 times the IQR.[42] Such outlying data points are represented by open circles. The dotted green line indicates the USG value of 1.035, whereas the shaded area indicates the reference interval for USG or serum creatinine concentration.

P < .0001); 518 (79%) became euthyroid (normal serum T_4 and TSH concentrations), whereas 137 (20.9%) developed either subclinical (n = 109) or overt (n = 28) hypothyroidism (low to low-normal T_4 with high TSH concentrations; Figure 1; Table S2).

A greater proportion of cats (17.1% vs 25.2%; P = .01) with pre-treatment USG <1.035 developed iatrogenic hypothyroidism than cats with USG ≥1.035 (Table S2).

3.4 | Clinically normal cats divided into groups based on UGS ≥1.035 vs USG <1.035

One hundred fifty-two (80%) of the 190 normal cats had concentrated USG (≥1.035) and 38 (20%) had moderately concentrated values (1.013-1.034). None had isosthenuric (1.008-1.012) or dilute (<1.008) values (Figure S1; Figure 5). Only 24 (12.6%), 16 (8.4%), and 9 (4.7%) cats had USG <1.030, <1.025, and <1.020 respectively (Figure S1).

The 38 cats with USG <1.035 were older than the 152 cats with USG ≥1.035 (median, 13 vs 11 years; P < .001), but did not differ in body weight (median, 4.8 vs 5.0 kg; P = .45). Compared with the 152 cats with USG ≥1.035, cats with USG <1.035 had higher serum creatinine concentrations (median, 1.7 mg/dL vs 1.5 mg/dL; P = .01), urea nitrogen (28.5 mg/dL vs 25 mg/dL; P = .002), and SDMA (11 μg/dL vs 10 μg/dL; P = .03).

3.5 | Comparison of ^{131}I-treated cats that developed azotemia vs remained nonazotemic to clinically normal cats

After ^{131}I treatment, 158 (24.1%) of the 655 hyperthyroid cats became azotemic and 497 (75.9%) remained nonazotemic (Figures 2 and 5).

The 158 cats that developed azotemia after ^{131}I treatment had lower pre-treatment USG than the 497 cats that remained nonazotemic (median, 1.021 vs 1.041 P < .0001; Figure 5A,B). The 158 azotemic cats also had lower post-treatment USG than did the 497 cats that remained nonazotemic (median, 1.018 vs 1.039; P < .0001; Figure 5A,B). Both groups of hyperthyroid cats had lower pre-treatment USG that did the 190 clinically normal cats (Figure 5A,B).

After ^{131}I treatment, USG decreased in the cats that developed azotemia (P < .0001), with 149 of the 158 (94.3%) azotemic cats having USG values <1.035 (Figures 2 and 5A). In contrast, USG did not change in the 497 cats that remained nonazotemic after treatment, but 190 (38.2%) had USG that remained <1.035 (Figures 2 and 4B). Both groups of hyperthyroid cats had lower post-treatment USG that did the 190 clinically normal cats (Figure 5A,B). Furthermore, ^{131}I treated cats (both azotemic and nonazotemic groups) had a higher proportion of USG <1.035 (94% and 38%, respectively) than did the clinically normal cats (20%; P < .0001; Figure 5A,B).

3.6 | Comparison of ^{131}I-treated cats that became euthyroid vs hypothyroid

The 137 cats that developed hypothyroidism after ^{131}I treatment were older and had higher pre-treatment serum creatinine, urea nitrogen, and SDMA concentrations than the 518 cats that became euthyroid (P < .005; Table S3). More of these cats also had pre-treatment USG <1.035 compared with euthyroid cats (56.9% vs 44.6%; P = .01; Table S3).

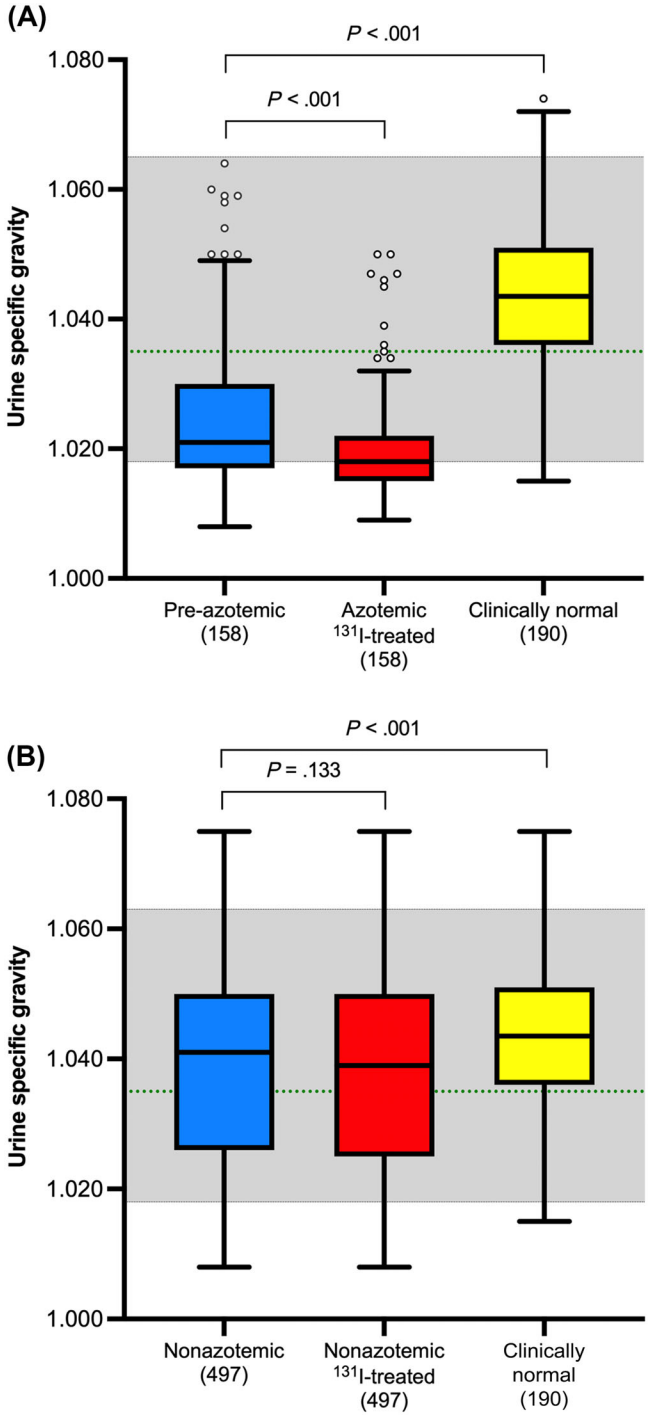

FIGURE 5 Boxplots of pre- and post-treatment urine specific gravity (USG) 655 hyperthyroid cats, divided into the 158 cats that developed azotemia after ^{131}I treatment and the 497 cats that remained nonazotemic. (A) Before and after USG in 158 cats that became azotemic and compared with USG values from 190 clinically normal cats; (B) Before and after USG in the 497 cats that remained nonazotemic, and compared with USG values from 190 clinically normal cats. See Figure 4 for key.

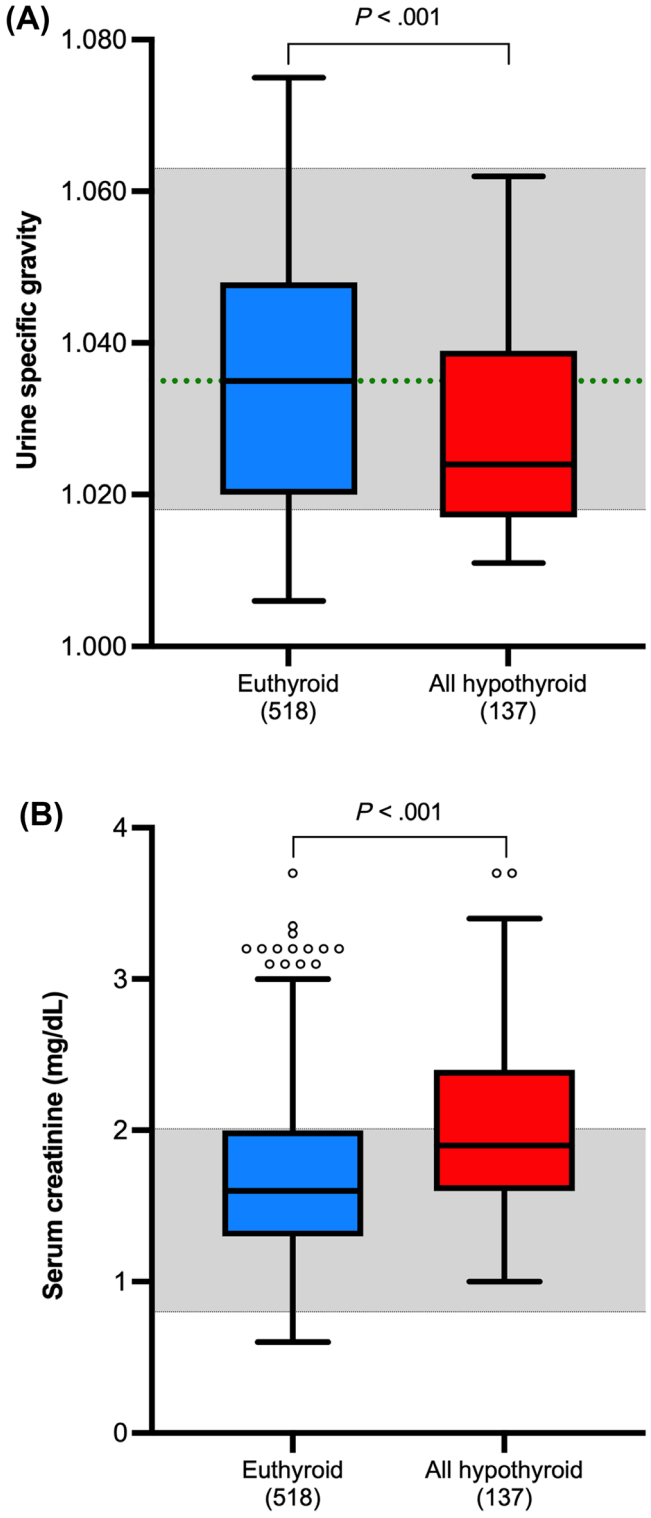

FIGURE 6 Boxplots of (A) post-treatment urine specific gravity (USG) and (B) serum creatinine concentrations in 655 hyperthyroid cats, divided into the 518 cats that became euthyroid vs the 137 cats that developed hypothyroidism (28 overt and 109 subclinical cats) after ^{131}I treatment. Figure 4 for key.

On pre-treatment thyroid scintigraphy, a greater proportion of the 137 hypothyroid cats had bilateral thyroid nodules than did the 518 euthyroid cats (59% vs 51.5%; $P = .05$; Table S4). A greater proportion of hypothyroid cats also had homogenous bilateral uptake than did euthyroid cats (22.6% vs 8.7%; $P < .001$) We detected no difference in the severity of hyperthyroidism in hypothyroid vs euthyroid

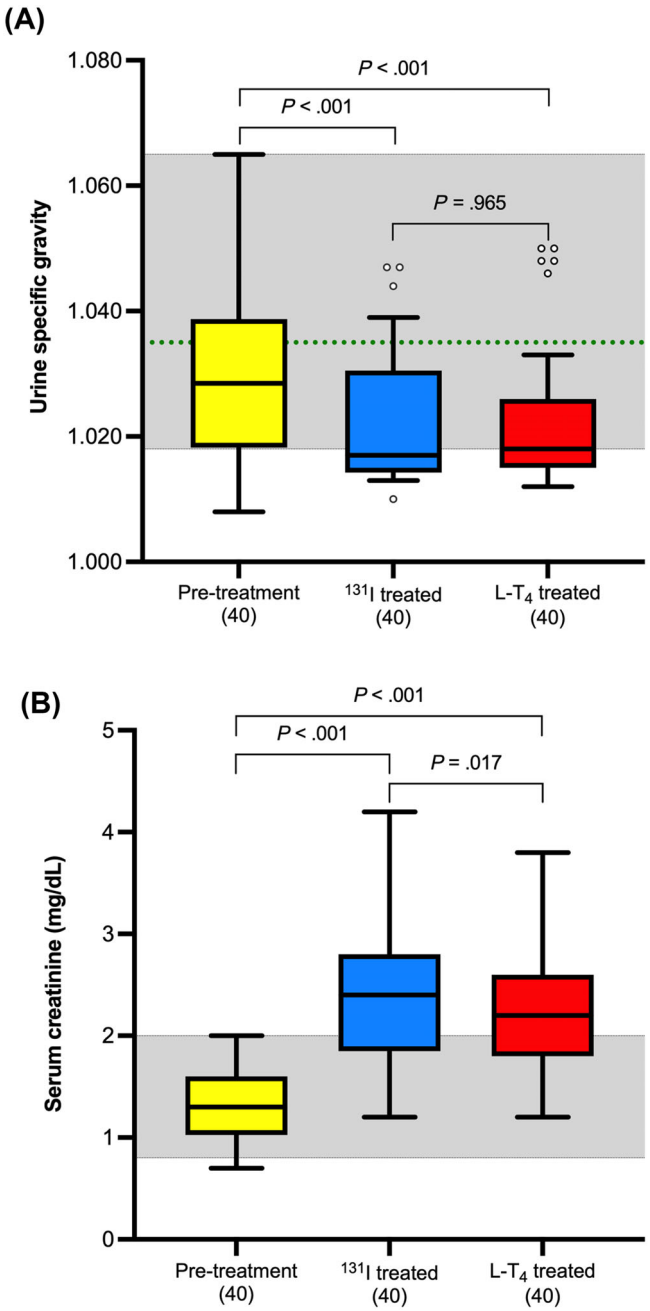

FIGURE 7 Boxplots of urine specific gravity values in 40 cats that developed ^{131}I-induced hypothyroidism and were treated with L-T_4. (A) USG values before ^{131}I when hyperthyroid, after ^{131}I when hypothyroid, and again on L-T_4 replacement therapy when euthyroid. (B) Serum creatinine concentrations before ^{131}I when hyperthyroid, after ^{131}I when hypothyroid, and again on L-T_4 replacement therapy when euthyroid. See Figure 4 for key.

cats (based on the overall dose or severity score),[36,37] but the 24-hour ^{131}I uptake was slightly higher in the hypothyroid cats (25% vs 23%; $P = .02$), resulting in a calculated ^{131}I dose that was lower for the hypothyroid cats than that in cats that became euthyroid (1.8 vs 1.9 mC; $P = .007$; Table S4).

After ^{131}I treatment, the 137 hypothyroid cats had higher serum creatinine, urea nitrogen, and SDMA concentrations and lower USG than did euthyroid cats (Table S5; Figure 6B). Hypothyroid cats had a 2.2-fold higher prevalence of azotemia than did the euthyroid cats (42.4% vs 19.3%; $P = .001$; Table S5). As expected, hypothyroid cats had lower serum T_4 and higher TSH concentrations than did the euthyroid cats ($P = .001$; Table S5).

Forty of the 137 hypothyroid cats had USG and serum creatinine concentrations measured again 3-6 months after euthyroidism was restored with levothyroxine treatment (Figure 7; Table S6). Of these 40 untreated hypothyroid cats, 12 had overt hypothyroidism (10 with azotemia) and 28 had subclinical hypothyroidism (20 with azotemia; Table S6). After levothyroxine supplementation, USG did not change, with 35/40 cats (87.5%) having USG values <1.035 (Figure 7A). Serum creatinine concentrations decreased after levothyroxine treatment, but 21/29 (72.4%) azotemic cats remained azotemic after euthyroidism was restored (Figure 7B). No difference in the response of overt vs subclinically hypothyroid cats was detected (Table S6).

3.7 | Sensitivity and specificity of pretreatment USG (≥1.035 vs <1.035) as a diagnostic test for masked CKD in hyperthyroid cats

In all 655 cats, the diagnostic test sensitivity of USG <1.035 as a predictor of masked, post-treatment azotemia was moderately high (86.1%) but the specificity was relatively poor (65.2%; Table 1).

TABLE 1 The diagnostic performance of pretreatment USG in detecting masked azotemia in 655 cats with untreated hyperthyroidism.

	No. of cats		
USG test result	**Pre-azotemic**	**Non-azotemic**	**Totals**
Positive < 1.035	136	173	309
Negative ≥ 1.035	22	324	346
Totals	158	497	655
Sensitivity (95% CI)	86.1 (79.7-91.1)		
Specificity (95% CI)		65.2 (60.8-69.4)	

Abbreviation: CI, confidence interval.

TABLE 2 The diagnostic performance of pretreatment USG in detecting masked azotemia in 518 cats with untreated hyperthyroidism rendered euthyroid after ^{131}I treatment.

	No. of cats		
USG test result	**Pre-azotemic**	**Non-azotemic**	**Totals**
Positive < 1.035	90	141	231
Negative ≥ 1.035	10	277	287
Totals	100	418	518
Sensitivity (95% CI)	90.0 (82.4-95.1)		
Specificity (95% CI)		66.3 (61.5-70.8)	

Abbreviation: CI, confidence interval.

TABLE 3 The diagnostic performance of pretreatment USG in detecting masked azotemia in 137 cats with untreated hyperthyroidism rendered hypothyroid after ^{131}I treatment.

	No. of cats		
USG test result	**Pre-azotemic**	**Non-azotemic**	**Totals**
Positive < 1.035	46	32	78
Negative ≥ 1.035	12	47	59
Totals	58	79	137
Sensitivity (95% CI)	79.3 (66.7-88.8)		
Specificity (95% CI)		59.5 (47.9-70.4)	

Abbreviation: CI, confidence interval.

When the cats were divided into euthyroid and hypothyroid groups, test sensitivity and specificity for USG <1.035 predicting post-treatment azotemia were similar. Compared to the hypothyroid cats, euthyroid cats had a slightly higher sensitivity (90% vs 79.3%; $P = .09$) and specificity (66.3% vs 59.5%; $P = .25$; Tables 2 and 3).

4 | DISCUSSION

Results of this study show that approximately half of untreated hyperthyroid cats have concentrated USG (≥1.035), whereas half have USG <1.035. After successful ^{131}I treatment, USG in most (81%) cats with pretreatment USG ≥1.035 remained unchanged. Similarly, USG in most cats (88%) with pretreatment USG <1.035 remained unchanged, with only 37/309 cats (12%) increasing USG to ≥1.035 after ^{131}I treatment. We could not determine the reason for the less-than-concentrated USGs in all of our hyperthyroid cats, but concomitant (masked) CKD was the most common cause, accounting for almost half of the cats (44%) with USG <1.035. Looking at only our treated cats that developed azotemic CKD, 86% (136/158) of these pre-azotemic cats had a pretreatment USG <1.035, and 96% (152/158) of these cats maintained a USG <1.035 after treatment when azotemic.

In addition to concurrent CKD, hyperthyroidism itself could potentially reduce urine concentrating ability through several mechanisms. These include hyperthyroid-induced primary polydipsia (compulsive water drinking),[47] resetting (lowering) of the plasma osmolality needed to stimulate thirst and arginine vasopressin secretion,[48] lowered sensitivity of the distal renal tubule to vasopressin,[49] reduced medullary sodium concentration secondary to increased renal blood flow and medullary washout,[50] or osmotic diuresis consequent to the increased filtered solute.[51,52] With all of these potential mechanisms, one might assume that restoring euthyroidism would resolve the underlying defect, leading to increased urine concentrating ability. Indeed, USG in the some of our hyperthyroid cats did become concentrated after successful treatment, but it failed to increase after treatment in 88% of the nonazotemic cats with a USG <1.035 in our study, suggesting that a cause other than hyperthyroidism is responsible for their persistent, sub-maximally urine concentration (USG < 1.035).

Values of USG <1.035 can be found in normal in cats, with between 10% to 20% of clinically normal cats having single (spot) USG values <1.035.[53-56] In agreement with those studies, 20% of our clinically normal, control cats (matched with our hyperthyroid cats for age, breed, and sex) had USG values <1.035. That said, the prevalence of USG values <1.035 in our ^{131}I-treated, nonazotemic cats remained almost 2-fold higher than that in our clinically normal cats (Figure 5B). Why urine concentrating ability appears to remain compromised in so many of our treated hyperthyroid cats that remain nonazotemic is unclear. Over half (54%) of these nonazotemic cats, however, had high-normal serum creatinine concentrations (≥1.6 mg/dL), so early, nonazotemic CKD (IRIS stage 1 or early stage 2)[57] might be responsible. Nevertheless, it appears that hyperthyroidism somehow induces a defect in urine concentration (not associated with overt CKD) in at least some hyperthyroid cats that is not always reversible after successful treatment.

Although the goal of ^{131}I treatment is to cure hyperthyroidism and restore euthyroidism, most current dosing protocols fail to achieve this goal, with 20% to 50% of ^{131}I-treated cats developing iatrogenic hypothyroidism after treatment.[9,32,36,38,58,59] Determination of thyroid status is of vital importance when assessing these ^{131}I-treated cats for CKD, because cats with iatrogenic hypothyroidism have a higher prevalence of azotemia than euthyroid cats,[2,14,25,32,36] as did the hypothyroid cats in this study (2.2-fold higher than our euthyroid cats; Figure 4B; Table S5). The azotemia that develops in cats with iatrogenic hypothyroidism, however, can sometimes be improved or even reversed with levothyroxine supplementation.[25,60] Although the mechanism(s) for how levothyroxine treatment resolves azotemia in hypothyroid cats is not completely known, the decrease in serum creatinine concentrations is likely related to a thyroid hormone-induced increase in GFR and renal blood flow, as described in levothyroxine-treated hypothyroid dogs[61] and humans.[62-64] The finding of azotemia in cats with iatrogenic hypothyroidism, therefore, might not always indicate renal azotemia (CKD), but might represent a pre-renal component associated with lowered GFR and renal blood flow, especially if USG is >1.035.[22,24,25] However, if azotemia and USG <1.035 persist after levothyroxine replacement has restored euthyroidism (evidenced by normal serum T_4 and TSH concentrations), then true renal azotemic CKD is highly likely.

Complicating this issue of azotemia and hypothyroidism is that impaired urine concentrating ability has been reported in some,[26,27] but not all,[28] studies of human hypothyroid patients, an effect that can sometimes be reversed with thyroid hormone treatment.[26,27] When we compared our hypothyroid and euthyroid cats, however, cats destined to become hypothyroid were older, had higher pretreatment serum concentrations of creatinine, urea nitrogen, and SDMA, with a higher proportion having pretreatment USG <1.035 (57% vs 45%; Table S3). After treatment, our hypothyroid cats continued to have higher serum concentrations of creatinine, urea nitrogen, and SDMA, as well as lower USG values. Compared to our euthyroid cats, hypothyroid cats had a higher proportion of post-treatment USG <1.035 (66% vs 48%), as well as azotemia (42% vs 19%; Table S4). Finally, when we evaluated hypothyroid cats supplemented with levothyroxine to restore euthyroidism, USG values failed to increase,

with 88% of cats maintaining a USG <1.035 (Figure 7A). Although serum creatinine concentrations decreased in hypothyroid cats that were treated with levothyroxine to restore euthyroidism, many remained azotemic, diagnostic for azotemic CKD (Figure 7B). Taken together, these findings strongly suggest that many hypothyroid cats develop USG values <1.035 as a result of concurrent (originally masked) CKD, rather than a direct effect of iatrogenic hypothyroidism on urinary concentrating ability itself.

In this study, hyperthyroid cats with concurrent (masked) CKD appeared to be at greater risk for developing iatrogenic hypothyroidism than did cats with normal renal function, a finding that was not expected. Our cats destined to become hypothyroid were older, had higher pretreatment serum concentrations of creatinine and urea nitrogen, and had a higher proportion having USG <1.035 (57% vs 45%; Table S3). These cats developed iatrogenic hypothyroidism despite being treated with a slightly lower ^{131}I dose than the cats that became euthyroid (1.8 vs 1.9 mCi). Since iodine (and therefore ^{131}I) is removed from the body primarily by renal excretion,[65,66] kidney disease can lead to decreased clearance and increased retention of ^{131}I, an effect which has been known for over 70 years.[67] The thyroid gland of patients with renal disease can continue to take up ^{131}I for a longer time than do those without renal disease, because they are presented with higher circulating concentrations of ^{131}I for a longer time.[68,69] Therefore, lowered doses of ^{131}I are generally recommended for human patients with known renal disease to help prevent overdosing with ^{131}I.[68-70] Although further studies of concurrent renal disease as a risk factor for ^{131}I-induced hypothyroidism are needed, lowering the administered ^{131}I dosage should be considered in hyperthyroid cats that have pretreatment USG <1.035, especially if they also have other known risk factors for ^{131}I-induced hypothyroidism.[37]

This study had several limitations. First of all, not all of our hyperthyroid cats were newly diagnosed, and half had been treated with methimazole. Although our study design required that methimazole be discontinued for at least 1 week before evaluation (when serum creatinine and USG were measured), standardizing the how long cats received methimazole or how well their hyperthyroidism had been controlled was not possible. Second, we did not follow our clinically normal cats longitudinally to exclude subclinical renal disease, especially in those with USG <1.035. Finally, finding a USG value <1.035 on a spot urine sample before-after treatment, as reported in this study, might not be sufficient to conclude that there is a defect in urine concentrating ability. Rather, assessing renal function is best done by measuring USG (along with serum creatinine concentrations) on multiple follow-up visits. Although serial measurements of USG after ^{131}I treatment was not part of our study design, we did in fact recheck most cats (both azotemic and nonazotemic) within the next 3-6 months after the post-treatment time reported in this paper. Almost all of these cats (>95%) maintained the USG measurement with the same range (>1.035 vs <1.035) as reported at 6-month post-treatment period (data not shown).

Is determination of pretreatment USG useful in predicting masked azotemic CKD in hyperthyroid cats? Many smaller studies have reported that detection of USG <1.035 alone in a "spot" urine sample is of little to no value for diagnosis of masked azotemic CKD in cats with untreated hyperthyroidism.[9,15,17] However, we know of 3 other prospective studies which reported that a USG <1.035 can indeed help predict which hyperthyroid cats will develop post-treatment azotemia.[1,2,10] In this study, the diagnostic test sensitivity of pretreatment USG <1.035 as a predictor of masked, post-^{131}I azotemia was moderately high (86%), meaning that few cats USG ≥1.035 subsequently developed azotemia; however, the specificity was relatively poor (65%), indicating that many cats with USG <1.035 would remain nonazotemic. Practically speaking, this means that almost half of hyperthyroid cats that have USG values <1.035 will go on to develop azotemic CKD after treatment, but half will remain nonazotemic. Finding a USG ≥1.035 makes masked CKD much less likely, developing in only 6.4% of our hyperthyroid cats that had concentrated USG values. When our cats were divided into euthyroid and hypothyroid groups, we found similar results for test sensitivity and specificity (Tables 2 and 3). Based on our data, we believe that USG, although not a good "diagnostic" test per se for masked CKD, helps us predict which cats are less likely to develop post-treatment azotemia, and allows clinicians to focus on cats that have a reasonable chance of developing post-treatment azotemia—information that can help clinicians appropriately manage these hyperthyroid cats.

ACKNOWLEDGMENT

No funding was received for this study. Presented as an oral abstract at the 2022 American College of Veterinary Internal Medicine Forum, Austin, Texas, Research Abstract Program.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Ethics approval (IACUC) was obtained before the study commenced.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Mark E. Peterson https://orcid.org/0000-0002-3016-1855
Mark Rishniw https://orcid.org/0000-0002-0477-1780

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Peterson ME, Rishniw M. Urine concentrating ability in cats with hyperthyroidism: Influence of radioiodine treatment, masked azotemia, and iatrogenic hypothyroidism. *J Vet Intern Med*. 2023;37(6):2039-2051. doi:10.1111/jvim.16849