

STANDARD ARTICLE

Radioactive iodine uptake in hyperthyroid cats after administration of recombinant human thyroid stimulating hormone

Amy E. Oberstadt¹ | Nathan C. Nelson¹  | Andrew K. Claude¹ | Kent R. Refsal² |
J. Catharine Scott-Moncrieff³ | Brian K. Petroff² | Daniel K. Langlois¹ 

¹Departments of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, Michigan, 48824

²Pathobiology and Diagnostic Investigation, College of Veterinary Medicine, Michigan State University, East Lansing, Michigan, 48824

³Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, Indiana, 47907

Correspondence

Daniel K. Langlois, Department of Small Animal Clinical Sciences, Michigan State University College of Veterinary Medicine, 736 Wilson Road, East Lansing, MI 48824. Email: langlo21@cvm.msu.edu

Present address

Nathan C. Nelson, Department of Molecular Biomedical Sciences, North Carolina State University College of Veterinary Medicine, Raleigh, NC 27607.

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Background: Radioactive iodine therapy is considered the treatment of choice for hyperthyroidism in cats, but the availability of this modality is limited by costs and hospitalization requirements. Administration of recombinant human thyroid stimulating hormone (rh-TSH) to humans with thyroid neoplasia or nodular goiter can increase thyroidal iodine uptake, thereby allowing the use of lower radioactive iodine doses for treatment. Veterinary studies of this subject are limited, and results are conflicting.

Objective: To investigate the effects of rh-TSH administration on thyroidal iodine uptake in hyperthyroid cats.

Animals: Ten client-owned hyperthyroid cats.

Methods: In this prospective clinical study, cats were administered saline (placebo), 50 µg rh-TSH (low-dose), and 100 µg rh-TSH (high-dose) in randomized crossover design with treatments separated by 7-10 days. After each treatment, thyroid scintigraphy was performed by administering 300 µCi ¹²³I and assessing radionuclide uptake 8 and 24 hours later. Serum thyroid hormone concentrations were measured at each visit.

Results: Thyroidal percent iodine uptakes (mean ± SD at 8 and 24 hours) in cats treated with placebo (25.2 ± 13.4%, 30.0 ± 12.8%), low-dose (24.1 ± 12.5%, 29.4 ± 13.7%), and high-dose rh-TSH (24.2 ± 16.3%, 30.8 ± 15.3%) were not different (*P* = .76). Independent of rh-TSH administration, percent iodine uptakes were positively correlated with serum thyroid hormone concentrations.

Conclusions and Clinical Importance: One-time administration of rh-TSH, even at high doses, would not be expected to lower radioactive iodine doses needed for treatment of hyperthyroidism in cats. Investigations of alternate strategies to increase thyroidal uptake of radioactive iodine are warranted.

KEYWORDS

¹²³I, ¹³¹I, hyperthyroidism, scintigraphy, therapy, Thyrogen

Abbreviations: MSU-VDL, Michigan State University Veterinary Diagnostic Laboratory; MSU-VMC, Michigan State University Veterinary Medical Center; RAIU, radioactive iodine uptake; rh-TSH, recombinant human thyroid stimulating hormone.

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1 | INTRODUCTION

Hyperthyroidism in cats is a debilitating and potentially life-threatening endocrine disorder that affects up to 10% of geriatric cats.¹ The hypermetabolic effects of untreated hyperthyroidism can

result in numerous adverse sequelae such as weight loss, behavioral changes, muscle wasting, malnutrition, heart disease, and hypertension, among others.² Although several treatment options exist, radioactive iodine therapy with ¹³¹I is widely considered to be the treatment of choice. A single treatment is curative in approximately 95% of cases, and complications are uncommon, occurring in less than 5% of cases.²⁻⁴

Despite these positive aspects, radioactive iodine therapy is not without limitations. Most treatment protocols require in-hospital isolation times of 3-9 days.^{4,5} Consequently, cats that are intolerable of prolonged isolation because of demeanor or concurrent medical conditions are poor candidates for ¹³¹I therapy. Treatment costs, which are currently \$1200-\$1900 at our institutions, also are prohibitive for many owners. Beyond these limitations, cat excreta remains radioactive for weeks and could be a source for human radiation exposure.^{5,6} Ideal dosing regimens for ¹³¹I have not been established, and protocols vary among institutions.^{3,4} Regardless, mechanisms to increase thyroidal radioactive iodine uptake (RAIU) would allow utilization of lower treatment doses, thereby addressing many current limitations. Recombinant human thyroid stimulating hormone (rh-TSH) administration has been shown to result in dose-dependent increases in thyroidal RAIU in humans.^{7,8} This strategy has been used in humans to reduce radioactive iodine doses for treatment of thyroid neoplasia and nodular goiter.⁸⁻¹⁰

The effects of TSH administration on RAIU are not well described in companion animals, and discordant results have been reported. Bovine TSH administration increases RAIU in healthy dogs.¹¹ However, these results were contradicted in another study in which rh-TSH administration had no effect on RAIU in dogs.¹² In a small pilot study of hyperthyroid cats, RAIU was increased by administration of 25 µg rh-TSH, but changes were heterogeneous and of questionable clinical utility.¹³ The authors speculated that increased rh-TSH doses could have resulted in greater and more consistent increases in RAIU.¹³ Indeed, an *in vitro* study has shown that responsiveness of feline thyroid cells to TSH is dose dependent, and hyperthyroid cells require higher TSH concentrations than do normal cells to stimulate cellular activity and thyroglobulin expression.¹⁴ Given current knowledge gaps, it is apparent that more detailed investigations of rh-TSH in hyperthyroid cats are warranted. The objective of this study was to investigate the effects of higher doses of rh-TSH on RAIU in cats with hyperthyroidism. In addition, potential associations of serum thyroid hormone concentrations with RAIU were investigated. We hypothesized that rh-TSH administration would result in dose-dependent increases in RAIU.

2 | MATERIAL AND METHODS

2.1 | Study design

A randomized, placebo-controlled, crossover study was conducted to investigate the effects of two doses of rh-TSH on RAIU in cats with hyperthyroidism. A sample size calculation was performed using data from previous studies.^{12,13,15} The analysis suggested 9 cats would be needed to detect an approximate 15% difference in RAIU

between rh-TSH doses with power of 0.8 and α of 0.05. Client-owned cats with hyperthyroidism were recruited from the Michigan State University Veterinary Medical Center and surrounding general practice clinics for enrollment between January 2017 and June 2017. External recruitment was accomplished by mailing promotional flyers to clinics within a 50 mile radius. Participating cats were required to have initial commercial laboratory (IDEXX, Antech, Michigan State University Veterinary Diagnostic Laboratory) confirmation of hyperthyroidism as evidenced by increased total T₄ concentrations within the previous 6 months in conjunction with compatible clinical signs. Inclusion also required a complete blood count, serum biochemical profile, urinalysis, and thoracic radiographs within 3 weeks of study enrollment. Cats were excluded if they had decreased appetite, body condition score of 1/9, increased serum creatinine concentrations (>1.6 mg/dL) increased serum bilirubin concentrations (>0.5 mg/dL), hematocrit <35%, gallop rhythm detected on auscultation, radiographic evidence of metastatic disease or cardiomegaly, and aggressive demeanor. Cats were not permitted to receive antithyroid medications during the study or within the 2 weeks preceding study commencement. No cats had been fed iodine restricted diets.

Cats were treated with IV administration of 2 mL 0.9% saline (placebo), 50 µg rh-TSH (low-dose), and 100 µg rh-TSH (high-dose) in randomized crossover design. Pharmaceutical grade rh-TSH (Thyrogen; Sanofi Genzyme, Cambridge, Massachusetts) was reconstituted with sterile saline, stored in aliquots of 50 or 100 µg at -20°C, and used within 14 weeks. Aliquots were allowed to thaw at room temperature immediately before use. Randomization order was determined using a random number generator (Microsoft Excel), and each treatment was separated by 7-10 days to allow sufficient washout for possible TSH effects.^{16,17} Thyroid scintigraphy examinations were performed after each treatment to assess RAIU.

2.2 | Thyroid scintigraphy

Thyroid scintigraphy examinations were performed using ¹²³I as described previously.^{13,18} One hour after rh-TSH/placebo administration, a 300 µCi dose of ¹²³I was administered PO followed by 3-4 mL of water to ensure passage of capsules into the stomach. Thyroidal RAIU was assessed using a planar gamma camera using a low energy, high-resolution collimator (Scintaron VI; Medical Imaging Electronics, Seth, Germany). Counts per minute were obtained with ¹²³I capsules immediately before capsule administration to allow for dosage calibration. A single ventral planar image of 200 000 counts was acquired with the cat in sternal recumbency at 8 hour (RAIU-8 hours) and 24 hour (RAIU-24 hours) time points after ¹²³I administration. Brief inhalant anesthesia with desflurane (Suprane; Baxter Healthcare, Deerfield, Illinois) in 100% oxygen was administered via face-mask to aid in scanning assessments. Areas of radionuclide uptake were selected using isocontour lines over the region of interest to determine counts per minute in that area. The RAIU was calculated as the percentage of the administered dose present in the thyroid lobes, corrected for physical decay of the dose using the following formula:

$$\% \text{ uptake} = \frac{\text{net counts per minute in thyroid}}{\text{decay} - \text{corrected net counts per minute in capsule}} * 100\%$$

Soft tissue attenuation correction was not performed because of the superficial location of the thyroid gland. Background correction was performed using background regions of interest drawn in the soft tissue adjacent to the thyroid gland. A single radiologist blinded to treatment group drew all isocontour lines and calculated all RAIU values.

2.3 | Serum hormone measurements

Before placebo or rh-TSH administration, blood samples were obtained at each visit ($n = 3$) from all cats for measurement of serum thyroid hormone concentrations, including free and total T_4 , total T_3 , and TSH. Collected samples were placed in serum collection tubes, and after clot formation, centrifuged for 10 minutes at 1200g. Serum was harvested and submitted to the Michigan State University Veterinary Diagnostic Laboratory for analysis. Serum concentrations of T_4 were measured with a commercially available radioimmunoassay kit (T_4 MAb Solid Phase Component System; MP Biomedicals LLC., Diagnostics Division, Orangeburg, New York). The volume of samples and reagents were used as per the manufacturer's protocol but the incubation period was extended to 2 hours in a 37°C water bath. The sensitivity of the assay, estimated as the mean concentration of T_4 at 90% specific binding (10 assays), was 3.4 nmol/L (range 3.1-4.0 nmol/L). Aliquots of feline serum with T_4 concentrations of 7 and 168 nmol/L were mixed in volume combinations of 9:1, 4:1, 1:1, 1:4, and 1:9 to assess parallelism. The results from assay of the mixtures showed respective percent observed/expected recovery rates of 82, 97, 99, 97, and 94%. When aliquots of a feline serum pool (14 nmol/L) were mixed with an added stock of 28, 57, 142, 226, and 255 nmol/L T_4 , the respective percent recovery rates were 147, 125, 118, 118, and 106%. Assay repeatability was determined from four pools of feline serum with mean T_4 concentrations of 8, 26, 65, and 160 nmol/L. The respective intra-assay percent coefficients of variation (CV) were 15.7, 11.9, 6.2, and 6.0% for 10 replicates. In 10 assay runs, the respective interassay percent CVs for each pool were 20.4, 11.9, 8.6, and 9.0%.

Serum concentrations of free T_4 were measured in dialysate with a commercially available kit including dialysis cells and a sensitive T_4 radioimmunoassay (Free T_4 - by Equilibrium Dialysis, Antech Diagnostics, Irvine, California) that previously has been described by the laboratory.¹⁹ Serum concentrations of total T_3 were measured with an in-house charcoal-separation radioimmunoassay where the procedures²⁰ and use in feline serum²¹ have been described elsewhere. Serum concentrations of TSH were measured with a solid-phase chemiluminescent immunometric assay (Immulite 2000 Canine TSH, Siemens Healthcare Diagnostics Ltd., Gwynedd, United Kingdom) previously validated for use in cats.²²

2.4 | Confirmation of rh-TSH bioactivity

Aliquots of rh-TSH were stored until after study completion to ensure that rh-TSH storage did not affect bioactivity. After completion of the study, rh-TSH stimulation testing was performed in 4 healthy cats using banked aliquots of rh-TSH. The aliquots, which had been stored at -20°C for 20 weeks, contained 50 µg rh-TSH. The cats were

members of a breeding colony and were deemed healthy on the basis of normal physical and laboratory examinations. The age and weight ranges of the cats were 2.5-7 years and 2.8-5.5 kg, respectively. Serum total T_4 concentrations were measured immediately before and 6 hours after IV administration of 50 µg rh-TSH. The mean \pm standard deviation (SD) total T_4 concentrations increased from a baseline of 24.3 ± 4.6 to 79.5 ± 9.2 nmol/L at 6 hours ($P < .001$). This 3-fold increase in total T_4 concentrations was within the expected range of responses for healthy cats,¹⁷ thus confirming the bioactivity of the rh-TSH used herein.

2.5 | Statistical analysis

Thyroidal iodine uptake data followed a normal distribution as assessed by Shapiro-Wilk testing and normal probability plot analysis and were reported as means \pm SD. Cats were further categorized into those with mild or severe biochemical hyperthyroidism on the basis of serum total T_4 concentrations <100 or ≥ 100 nmol/L, respectively. The iodine uptake data were evaluated by a split-plot analysis of variance with the grouping factor of hyperthyroidism grade (mild or severe) and the repeat factors of time of scanning (8 or 24 hours), treatment dose, and study period. Nonsignificant factors and their interactions were deleted from the model, resulting in the final split-plot analysis of variance with the grouping factor of grade and the repeat factor of time of scanning. Simple linear regression analysis and calculation of the coefficient of determination, or R-squared (R^2), were performed to further investigate relationships between thyroidal iodine uptake and serum thyroid hormone concentrations. Statistical analyses were performed using commercially available software (SAS, version 9.3; SAS Institute Inc, Cary, North Carolina), and for all analyses, $P \leq .05$ was considered significant.

3 | RESULTS

Ten cats, 5 spayed females, and 5 neutered males met inclusion criteria and participated in the study. The median age of the cats was 11.5 years (range 10-17 years), and the median weight was 4.7 kg (range 2.1-6.3 kg). All 10 cats had increased total T_4 concentrations and suppressed TSH concentrations. The mean \pm SD total T_4 concentration of 129.7 ± 53.1 nmol/L at study commencement (visit 1) was nearly identical to the mean \pm SD total T_4 concentration of 127.3 ± 43.7 nmol/L at the third and final visit ($P = .803$). Three cats were considered to have mild biochemical hyperthyroidism (total $T_4 < 100$ nmol/L) whereas 7 cats were considered to have severe biochemical hyperthyroidism (total $T_4 > 100$ nmol/L). Eight cats completed all 3 study phases whereas 2 cats completed 2 of 3 study phases. In 1 cat, this was because of vomiting of ^{123}I capsule contents shortly after administration. The other cat experienced esophageal retention of capsule contents that was detected on the 8-hour scintigraphy scan. The RAIU data from these visits, both of which were after 50 µg rh-TSH administration, were excluded from analyses.

Cats received mean \pm SD dosages of 13.01 ± 5.16 and 26.02 ± 10.31 µg/kg for low-dose and high-dose rh-TSH protocols, respectively. Thyroid scintigraphy examinations did not reveal differences in thyroidal RAIU in placebo, low-dose, and high-dose treatment

groups at either 8- or 24-hour time points (Figure 1; $P = .76$). There were 36 assessments of RAIU in the rh-TSH administration groups (16 after low-dose and 20 after high-dose) when considering both 8- and 24-hour time points. Compared to corresponding placebo treated cats, percent RAIUs were increased in 13 instances (range, 0.3%-18%) and decreased in 23 instances (range, 0.2%-10.9%). In 3 of 36 instances, the percent RAIU change was >8%. One cat (severe hyperthyroidism group) with RAIU-8 hours of 37.5% after high-dose rh-TSH administration had a placebo RAIU-8 hours of 19.2%. Another cat (severe hyperthyroidism) with RAIU-8 hours of 56.6% after high-dose rh-TSH administration had a placebo RAIU-8 hours of 45.4%. Conversely, one cat (severe hyperthyroidism) with RAIU-8 hours of 24.7% after high-dose rh-TSH administration had a placebo RAIU-8 hours of 35.6%. All other percent RAIU differences were $\leq 8\%$.

Cats with severe biochemical hyperthyroidism (total $T_4 > 100$ nmol/L) had greater RAIU than cats with mild hyperthyroidism ($P = .02$). Associations of RAIU with the severity of biochemical hyperthyroidism were further investigated through linear regression and calculation of R^2 . Serum total T_4 , free T_4 , and total T_3 concentrations were positively and significantly correlated with RAIU-8 hours (Figure 2). Serum concentrations of total T_4 ($R^2 = 0.222$, $P = .17$) and total T_3 ($R^2 = 0.163$, $P = .25$) were not significantly correlated with RAIU-24 hours, but free T_4 concentrations maintained a positive, albeit weaker, relationship with RAIU at 24 hours ($R^2 = 0.399$, $P = .05$).

4 | DISCUSSION

In this study of 10 cats with naturally occurring hyperthyroidism, 50 and 100 μg doses of rh-TSH failed to consistently increase

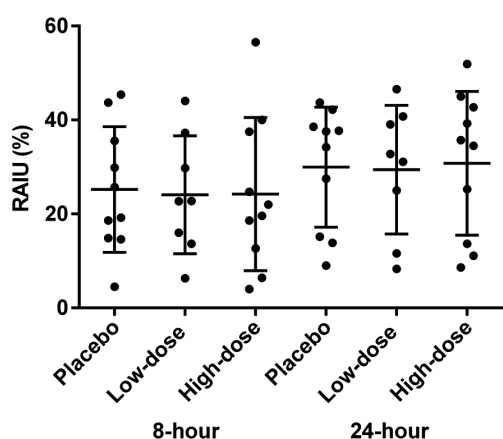


FIGURE 1 Scatterplot depicting radioactive iodine uptake (RAIU) in hyperthyroid cats after treatment with saline (placebo, $n = 10$), 50 μg recombinant human thyroid stimulating hormone (rh-TSH) (low-dose, $n = 8$), and 100 μg rh-TSH (high-dose, $n = 10$). The center and outer horizontal lines represent mean and standard deviation (SD), respectively. The RAIUs were calculated at 8- and 24-hour time points after 300 μCi ^{123}I administration. The uptakes (mean \pm SD at 8 and 24 hours) in placebo ($25.2 \pm 13.4\%$, $30.0 \pm 12.8\%$), low-dose ($24.1 \pm 12.5\%$, $29.4 \pm 13.7\%$), and high-dose ($24.2 \pm 16.3\%$, $30.8 \pm 15.3\%$) treatment groups were not different ($P = .76$)

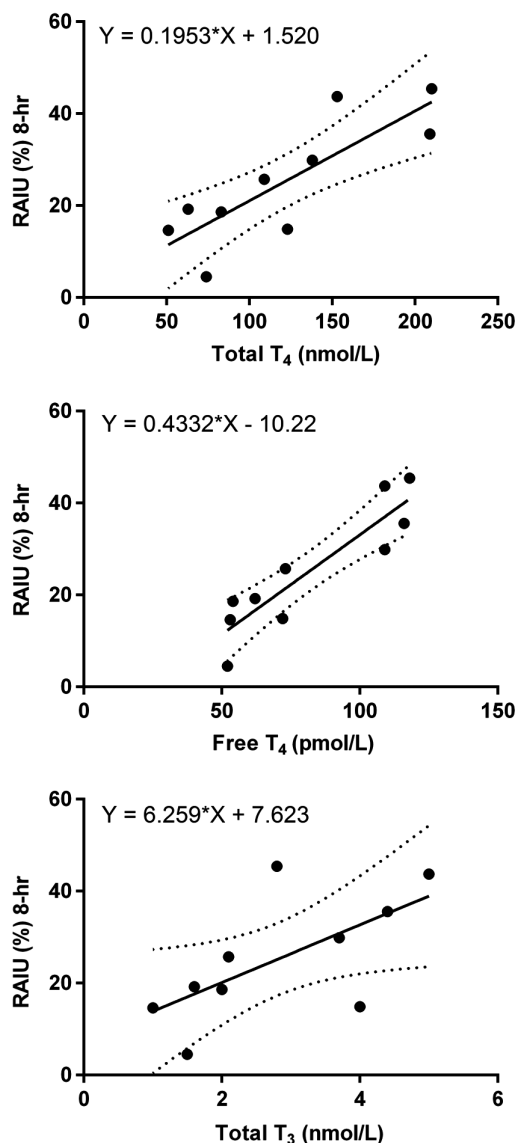


FIGURE 2 Scatterplot with linear regression line to investigate correlations between serum thyroid hormones and thyroidal radioactive iodine uptake (RAIU). The RAIU was calculated at 8 hours after 300 μCi ^{123}I administration. Both hormone concentrations and RAIU-8 hours values are from the placebo (non-rh-TSH) treatment group. The serum concentrations of total T_4 ($R^2 = 0.689$, $P = .003$), free T_4 ($R^2 = 0.819$, $P < .001$), and total T_3 ($R^2 = 0.420$, $P = .04$) were all positively correlated with RAIU-8 hours. The equation for each regression is in the upper left corner. The dotted lines surrounding the regression line represent the 95% confidence band of the best-fit line

thyroidal RAIU. In humans with nodular goiter, single dose administration of 10 or 30 μg rh-TSH doubles 24 hour RAIU.²³ Therefore, rh-TSH administration can be used to achieve 50%-60% reductions in radioiodine doses in humans with nodular goiters.⁸ Recombinant human TSH administration also can be used in a similar manner in humans to facilitate thyroidal remnant ablation for incompletely excised or metastatic thyroid cancer after thyroidectomy.²⁴ This strategy also obviates the need for cessation of thyroid supplementation before radioiodine therapy.¹⁰ The results of our study suggest that rh-TSH administration is unlikely to have any benefit for the treatment of hyperthyroidism in cats. The reasons for this lack of effect in cats

are unknown, but it is possible that feline adenomatous thyroid tissue does not respond to TSH. This would be consistent with previous reports in which TSH stimulation testing failed to consistently increase serum thyroid hormone concentrations in hyperthyroid cats.^{13,25,26}

It is noteworthy that our findings contradict the results of a previous study of 5 hyperthyroid cats in which increases in RAIU were reported in response to 25 µg rh-TSH administration.¹³ There were several methodologic differences between studies that might account for the different results. In this study, we randomized treatment order, used higher rh-TSH doses, and blinded our radiologist to treatment group. The times of scanning in relation to rh-TSH and ¹²³I administration also were slightly different. It is unknown if these or other factors are responsible for the discrepancies. In the previous report, RAIU increased by 20% in one cat in response to rh-TSH. In our study, only 1 of 10 cats experienced a change of similar magnitude which occurred at the 8-hour time point (19.2%-37.5% RAIU) after 100 µg rh-TSH administration. Interestingly, most cats in our report actually experienced decreases in RAIU after both 50 and 100 µg rh-TSH administration. Differences in RAIU among treatment groups were trivial in the majority of cats. As such, the authors believe that differences in RAIU in individual cats are likely a result of intrasubject variation that is independent of any true rh-TSH effect. Regardless, even if the rh-TSH administration did increase the RAIU percent by a value between 0% (reported herein) and 7% (reported previously), the effect would not be of clinical relevance.

The possibility of alternate rh-TSH administration protocols resulting in increased RAIU cannot be excluded. For instance, the typical rh-TSH dosing protocol used for thyroid remnant ablation in humans is 2 doses of 900 µg, given 24 hours apart, followed by ¹³¹I administration 24 hours later.²⁴ A similar protocol in veterinary medicine would offset the potential cost-saving benefits and reduction in hospitalization times that could be achieved with a one-time rh-TSH administration protocol. Furthermore, it is unknown if repeated rh-TSH administration could recruit previously atrophied nondiseased thyroid tissue and increase the risk of treatment-induced hypothyroidism. One study of humans with nontoxic nodular goiter suggested maximum increases in RAIU in response to rh-TSH actually occurred the day after rh-TSH administration.²³ It is possible that a delayed effect also could occur in hyperthyroid cats. However, significant increases in RAIU are still observed on the day of rh-TSH administration in humans with nontoxic nodular goiter,²³ and increases in thyroidal technetium pertechnetate uptake also have been observed in healthy cats on the day of rh-TSH administration.¹⁵ If single-dose rh-TSH affected RAIU in hyperthyroid cats, it would be expected that some effect, even if submaximal, would have been observed in our study. Nonetheless, investigation of alternate timing strategies would be needed to confirm or refute these speculations.

Current radioactive iodine treatment protocols vary among institutions. Some institutions use fixed dose protocols with doses ranging from 2 to 5 mCi of ¹³¹I.^{3,4,27} Others use dose calculations that incorporate various clinical and imaging parameters.³ Regardless, any strategy that could result in consistent increases in the percent uptake of radioactive iodine would theoretically lead to ¹³¹I dose reductions. One alternative strategy to achieve this aim would be dietary iodine

restriction before ¹³¹I therapy to reduce available iodine and create an environment for optimal radioiodine uptake.^{18,28} Dietary iodine restriction has been recommended for 5 days to 4 weeks preceding ¹³¹I administration in humans with thyroid carcinoma.²⁸ There is evidence that dietary iodine restriction can alter RAIU in hyperthyroid cats, but this intriguing premise requires further investigation.¹⁸

Although not a primary study aim, we did observe positive correlations between serum thyroid hormones and RAIU. Serum total T₄, free T₄, and total T₃ were positively correlated with RAIU at 8 hours, but only free T₄ concentrations remained significantly correlated at 24 hours. Similar relationships have been reported previously in hyperthyroid cats, and thyroid hormone concentrations also have been shown to positively correlate with estimated thyroid volume.²⁹ As such, the increasing RAIU with increasing thyroid hormone concentrations may simply be a result of a greater mass of hyper-functioning thyroid follicular cells. The exact clinical significance of this relationship is unknown, but it seems logical that cats with more severe disease and larger goiters have greater RAIU than do those with less severe disease and smaller goiters. This may partially explain why fixed dose ¹³¹I protocols have been reported to have similar cure rates as compared to protocols in which dose calculations are performed for individual cats.³

In summary, thyroidal RAIU in hyperthyroid cats was not increased by administration of 50 and 100 µg doses of rh-TSH. Consequently, single-dose rh-TSH administration would not be expected to lower the doses of ¹³¹I needed for definitive treatment of hyperthyroidism in cats. Consistent with previous reports, RAIU is positively correlated with the degree of biochemical hyperthyroidism. Additional studies are needed to further refine current ¹³¹I treatment protocols and to assess alternative methods for increasing thyroidal RAIU.

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CONFLICT OF INTEREST

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

This study was approved by the Michigan State University IACUC (approval numbers 02/17-015-00 and 07/17-122-00).

ORCID

Nathan C. Nelson  <https://orcid.org/0000-0003-3765-1694>

Daniel K. Langlois  <https://orcid.org/0000-0001-7726-6307>

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