# Assessment of Renal Function in Hyperthyroid Cats Managed with a Controlled Iodine Diet

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**KEY WORDS:** Feline, hyperthyroid cats, controlled iodine

**ABBREVIATIONS**:

$^{99m}$Tc-DTPA: $^{99m}$Technetium diethylenetriaminepentaacetic acid
CLEIA: Chemiluminescent enzyme immunoassay
CKD: Chronic kidney disease
CBC: Complete blood count
EMD: Epaxial muscle diameter
EDTA: Ethylenediaminetetraacetic acid
ERD: Semi-quantitative feline specific albuminuria assay
$fT_4$ED: Free thyroxine by equilibrium dialysis
$fT_3$: Free triiodothyronine
GGT: Gamma-glutamyl transpeptidase
GFR: Glomerular filtration rate
$^{131}$I: Radioiodine
mCi: Millicuries
SCr: Serum creatinine
SDMA: Symmetric dimethylarginine
SD: Standard deviation
SBP: Systolic blood pressure
$TT_3$: Total triiodothyronine
TSH: Thyroid stimulating hormone
$T_4$: Thyroxine
$TT_4$: Total thyroxine
$T_3$: Triiodothyronine
UAC: Urine albumin to creatinine ratio
UPC: Urine protein to creatinine ratio
UGGTC: Urine gamma-glutamyl transpeptidase to creatinine ratio

## ABSTRACT

**Background:** Previous studies have demonstrated that glomerular filtration rate (GFR) declines following treatment of hyperthyroidism independent of treatment modality. The post-treatment effects of Hill's Prescription Diet y/d Feline on renal function and muscle mass have not been evaluated.

**Hypothesis:** Treatment of feline hyperthyroidism with y/d will create a euthyroid state with a decrease in renal function and an increase in muscle mass.

**Animals:** Fifeteen client-owned cats with naturally occurring hyperthyroidism.

**Methods:** Prospective observational study.

Hyperthyroidism was confirmed via elevated total thyroxine ($TT_4$) concentration. Baseline excretory renal function was assessed via GFR, serum creatinine (SCr) concentration, serum symmetric dimethylarginine (SDMA) concentration, and urinalysis. Ultrasound was used to measure epaxial muscle diameter (EMD). Baseline parameters were re-assessed 6-months after feeding exclusively y/d.

**Results:** There was a significant decline in both $TT_4$ (mean pre 185.5 nmol/l, post 60.5 nmol/l, $p < 0.001$) and SCr (mean pre 1.11mg/dl, post 0.93 mg/dl, $p < 0.001$) 6-months post-treatment. No change in GFR (mean pre 2.31 ml/min/kg, mean post 2.26 ml/min/kg, $p = 0.71$), SDMA (mean pre 12.47 µg/dl vs. mean post 12.26 µg/dl, $p = 0.41$), or EMD (mean pre left: 1.56 cm, right 1.55 cm, $p = 0.95$, mean post left: 1.62 cm, right 1.56 cm, $p = 0.45$) was observed. SDMA was better correlated with GFR than SCr ($r = 0.71$ vs. 0.55, $p = 0.04$).

**Conclusions and Clinical Importance:** Management of feline hyperthyroidism with Hill's y/d Feline over 6-months significantly reduced $TT_4$ however mean $TT_4$ remained above the reference interval. There was no change in GFR or muscle mass.

## INTRODUCTION

Since its recognition in the late 1970's,[1] hyperthyroidism has become the most commonly diagnosed endocrinopathy in older cats. Treatment modalities have classically included anti-thyroid medication (methimazole or carbimazole), thyroidectomy, and radioiodine (131I) therapy. Previous studies have demonstrated that glomerular filtration rate (GFR) significantly declines following treatment of hyperthyroidism independent of treatment modality.[2,3,4,5] Recently, Hill's Prescription Diet y/d Feline, a controlled iodine food, with reduced phosphorus and protein and increased omega-3 fatty acids, has been introduced as a reversible treatment option for management of feline hyperthyroidism.[6,7] In client-owned hyperthyroid cats, feeding y/d Feline led to a significant decline in $TT_4$ concentrations between 1 and 6 months, without adverse effects.[8,9] In contrast to other treatment modalities, the serum creatinine (SCr) concentration in cats fed the iodine-controlled diet, significantly decreased between 1 and 6 months of dietary therapy.[8,9] Additional effects of y/d Feline on renal excretory function in hyperthyroid cats have not been evaluated.

GFR measurement is considered the gold standard for evaluating renal excretory function, and is often measured using plasma clearance techniques. Due to time, labor, and expense, plasma clearance techniques that approximate GFR are not routinely performed in practice. SCr concentration is the most commonly assessed renal excretory function parameter, however, loss of muscle mass in hyperthyroid cats leads to a decrease in the amount of creatinine produced, potentially decreasing SCr. Symmetric dimethylarginine (SDMA) is a byproduct of protein methylation that is largely excreted by the kidneys.[10] In people, serum SDMA correlates with GFR and appears to be a more sensitive biomarker than SCr for assessing renal dysfunction.[11] Recently, an inverse linear relationship was found between increasing serum SDMA and declining GFR in cats with chronic kidney disease (CKD).[12] In addition, there is evidence that serum SDMA is a sensitive biomarker for CKD in cats; allowing earlier recognition of CKD compared with SCr concentration.[13]

The first aim of this study was to evaluate the effects of y/d Feline on renal function in client-owned cats with natural occurring hyperthyroidism after 6 months of treatment. The second aim was to evaluate the effects of the controlled-iodine food on overall muscle mass via ultrasonographic evaluation of the epaxial muscle diameter (EMD). It was hypothesized that controlled dietary iodine as a treatment for hyperthyroidism would create a euthyroid state with a decrease in renal function and an increase in muscle mass.

## MATERIALS AND METHODS

### Animals

Cats were recruited from the Kansas State

University Veterinary Health Center patient population and surrounding primary care veterinary hospitals. The Institutional Animal Care and Use Committee of Kansas State University approved the study and written owner consent was obtained prior to patient entry into the study.

**Inclusion Criteria**

Newly diagnosed, or previously diagnosed hyperthyroid cats on anti-thyroid medication were eligible for inclusion. Anti-thyroid medication was discontinued at least 1week prior to inclusion. Hyperthyroidism was confirmed by elevated $TT_4$ concentration measured via chemiluminescent enzyme immunoassay (CLEIA)[a], a Michigan State University (MSU) thyroid function panel ($TT_4$, $TT_3$, $fT_4ED$, $fT_3$, and TSH)[b] and thyroid technetium scan.

**Exclusion Criteria**

Cats were excluded from the study if previously treated with $^{131}I$, or evidence of significant comorbidities (diabetes mellitus, neoplasia, CKD). In addition, cats were excluded if a fractious temperament prevented frequent handling or multiple sample collections. Finally, cats were excluded if they refused to reliably eat the diet, or if a lack of strict dietary compliance was reported.

**Study Design**

A 6-month, prospective, observational study was conducted. Cats that fulfilled the inclusion criteria were transitioned over the course of 1 week to Hill's y/d Feline dry and/or canned formulations, based on cat/owner preference. Owners were provided instructions detailing diet transition guidelines with the goal of meeting the cats resting energy requirements (RER). RER was calculated as a minimum daily requirement for each cat using the equation 1.4[(30 x body weight (kg) + 70], with owners instructed not to restrict the cat to this amount if more food was desired. In addition, food storage information was provided to help ensure no cross-contamination with other products that could contain iodine. Each cat was re-evaluated 1, 2, 3, and 6-months after eating y/d Feline exclusively. The cats' willingness to eat the food, and owners' ability to maintain strict dietary compliance was discussed at each visit.

**Initial Hospital Visit**

Initial evaluation to confirm the diagnosis of hyperthyroidism and to rule out co-morbidities included physical examination, body weight, CLEIA $TT_4$ concentration[a], MSU thyroid function panel[b], complete blood count (CBC), serum biochemistry, serum SDMA[c], urinalysis, aerobic bacterial urine culture, urine protein to creatinine ratio (UPC), urine gamma-glutamyl transpeptidase (GGT) to creatinine ratio (UGGTC), semi-quantitative feline specific albuminuria assay (ERD)[d], Doppler[e]-measured systolic blood pressure (SBP), thyroid technetium scan, plasma clearance of $^{99m}$Tc-DTPA, and ultrasound assessment of EMD and thyroid gland volume.

**Subsequent Hospital Visits**

Evaluation at 1 and 3-months included physical examination, body weight, CLEIA $TT_4$ concentration[a], CBC, serum biochemistry, serum SDMA[c], urinalysis, UPC, UGGTC, ERD[d], and SBP[e]. The 2-month evaluation included CLEIA $TT_4$ concentration to help document continued dietary compliance, and the final 6-month evaluation included all diagnostics performed at 1 and 3-months in addition to repeating the extended thyroid panel[b], $^{99m}$Tc-DTPA plasma clearance, and ultrasonographic assessment of EMD and thyroid gland size. All ultrasonographic assessments of the epaxial muscles and thyroid glands were performed by the same board certified radiologist (LA).

**Blood and Urine Sample Collection and Analysis**

Blood samples were collected from the jugular or medial saphenous vein. All urine samples were collected by cystocentesis. Serum was stored at -80°C from each recheck evaluation and SDMA concentrations measured as previously described.[13] Urinalyses were performed using a commercially available reagent strips[f], refractometer for USG, and standard microscopic sediment examination. Approximately 2 mL of urine

were collected for the ERD[d], which was interpreted as either negative, low positive, medium positive, or high positive. For ease of analysis, the results were scored as follows: negative = 0, low positive = 1, medium positive = 2, and high positive = 3. Approximately 0.5 mL of urine was saved from each urine sample and refrigerated until submitted, within 2 hours, for aerobic culture and sensitivity (initial evaluation and as indicated by urine sediment evaluation on subsequent evaluations). Urine protein was quantified using the benzethonium chloride reaction method and urine creatinine was quantified using the buffered Jaffe reaction, both with an automated chemistry analyzer[g]. The UPC was calculated from this data for each urine sample. Urine GGT was quantified using an enzymatic colorimetric assay[h] with an automated chemistry analyzer, and the UGGTC was then calculated using the same urine creatinine value for the UPC calculation.

**Blood Pressure Measurement**

Systolic blood pressure measurements were obtained via ultrasonic Doppler[e] monitor after the cats were acclimated to the hospital environment. Cats were placed in lateral recumbency and the up forelimb was used for pressure measurement with a cuff width approximately 35-40% the circumference of the leg, placed directly below the elbow. After clipping directly over the common digital branch of the radial artery, 3-4 readings were obtained and the mean was recorded. At subsequent blood pressure measurements, the same body position, limb, and cuff size were used. Cats that had persistent hypertension (systolic blood pressure >180mmHg on ≥ 2 measurements at least 1 week apart) were started on once daily oral amlodipine[i] at 0.625mg per cat, with the dosage adjusted as needed upon reevaluation.

**Imaging**

The same board-certified veterinary radiologist (LA) performed all ultrasonographic evaluations of the left and right epaxial muscles and thyroid glands. When required, ketamine (5mg/kg, IV) and diazepam (0.5mg/kg, IV) were administered for sedation. For the EMD, three measurements of the maximal epaxial diameter were taken at the level of lumbar vertebrae 3-4, and the mean was recorded. For the thyroid gland, the maximum width, height, and length of each lobe was used to calculate each thyroid lobe volume (mm3) as previously described[14] using the formula $\pi/6$[length (mm) x width (mm) x height (mm)]. The total thyroid volume for each cat was then estimated by summing the volume of the right and left thyroid lobes. Thyroid scintigraphy was performed as previous described.[15] The thyroid to zygomatic salivary gland ratio was calculated for both thyroid glands, and a ratio > 1.2:1 was considered consistent with hyperthyroidism.[16] Unilateral disease was defined as one thyroid gland with a thyroid to salivary gland ratio >1.2:1 and bilateral disease was defined as both thyroid glands with a thyroid to salivary gland ratio >1.2:1.

**Determination of GFR**

Glomerular filtration rate was determined by analysis of a $^{99m}$Tc-DTPA plasma disappearance curve. Baseline plasma clearance studies were performed on the second day of initial evaluation, after results of screening blood and urine tests had been obtained. Doses of $^{99m}$Tc-DTPA for injection and for a standard were drawn and measured in millicuries (mCi) by use of a dose calibrator. The standard was prepared by placing approximately 1 mCi of $^{99m}$Tc-DTPA in a volumetric flask and adding water to make a total volume of 1 L. Approximately 1 mCi of 99mTc-DTPA was administered via the cephalic or medial saphenous vein. Pre- and post-injection syringe activity was counted using a scintillation probe to determine the exact dose of radioisotope administered. Time zero was recorded. Blood samples were collected via jugular vein, or the medial saphenous vein opposite the injection site at 15, and 120 minutes.[17] Plasma was harvested from centrifuged blood anticoagulated with ethylenediaminetetraacetic acid (EDTA). One-milliliter aliquots of the diluted standard and plasma samples were

***Table 1.*** *$TT_4$ concentrations over time as measured by CLEIA*

| Patient | Baseline | 1-month | 2-month | 3-months | 6-month |
|---|---|---|---|---|---|
| 1 | 436 | 79.7 | 58.9 | 48.6 | 55 |
| 2 | 236 | 265 | 112 | 85.2 | 59 |
| 3 | 128 | 56.1 | 41.8 | 51.2 | 39.8 |
| 4 | 66.8 | 32.3 | 18.8 | 46.7 | 33.8 |
| 5 | 426 | 56.1 | 54.7 | 73 | 78.8 |
| 6 | 421 | 118 | 69.5 | 136 | 176 |
| 7 | 62.3 | 19.7 | 21.1 | 11 | 19.1 |
| 8 | 72.6 | 44.3 | 39.1 | 42.7 | 46.9 |
| 9 | 149 | 46.9 | 46.3 | 57.7 | 72.6 |
| 10 | 236 | 71.6 | 57 | 66.5 | 54.4 |
| 11 | 90.1 | 42.9 | 37.8 | 62.2 | 67.7 |
| 12 | 82 | 45.3 | 46 | 52.1 | 43.2 |
| 13 | 136 | 38.2 | 39.7 | 34.8 | 54 |
| 14 | 185 | 39.7 | 64.1 | 86.1 | 64.2 |
| 15 | 56.3 | 60 | 81.6 | 54.6 | 43 |
| **Mean** | **185.54** | **67.72** | **52.56** | **60.56** | **60.5** |

***Reference Interval 10-45 nmol/L***

***Table 2.*** *MSU thyroid function panel results*

| Case No. | $TT_4$ (nmol/L) | | $TT_3$ (nmol/L) | | $fT_4ED$ (pmol/L) | | $fT_3$ (pmol/L) | | TSH (mU/L) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Initial | 6 Month | Initial | 6 Month | Initial | 6 Month | Initial | 6 Month | Initial | 6 Month |
| 1 | >156 | 54 | 4.1 | 2.6 | >128 | 35 | 10.8 | 5.7 | 0 | 8 |
| 2 | >156 | 59 | >4.7 | 1.8 | >128 | 46 | 9.6 | 5 | 0 | 0 |
| 3 | 95 | 48 | 1.4 | 1.1 | 105 | 46 | 4.2 | 2.1 | 9 | 0 |
| 4 | 73 | 40 | 1.5 | 1.4 | 53 | 43 | 2.4 | 2 | 0 | 0 |
| 5 | >156 | 68 | 4 | 1.9 | >128 | 60 | 9.6 | 2.4 | 0 | 0 |
| 6 | >156 | 125 | 3.7 | 2.9 | >128 | >128 | 17.4 | 5 | 9 | 0 |
| 7 | 79 | 18 | 0.9 | 0.4 | 69 | 27 | 1.2 | 1 | 8 | 0 |
| 8 | 50 | 47 | 1.1 | 0.8 | 64 | 35 | 2.3 | 1.8 | 0 | 0 |
| 9 | 101 | 63 | 2.5 | 2 | 104 | 55 | 6.8 | 4.3 | 0 | 0 |
| 10 | >156 | 56 | 3.1 | 2.2 | >128 | 59 | 8.4 | 4.8 | 0 | 0 |
| 11 | 77 | 59 | 0.9 | 0.8 | 73 | 49 | 1.8 | 2.2 | 0 | 0 |
| 12 | 64 | 33 | 1 | 0.7 | 74 | 44 | 3.1 | 1.2 | 0 | 0 |
| 13 | 96 | 60 | 2 | 1.4 | >128 | 63 | 2.6 | 3.2 | 0 | 7 |
| 14 | 116 | 79 | 1.6 | 1.9 | 110 | 57 | 2.7 | 5.4 | 0 | 0 |
| 15 | 67 | 58 | 1.1 | 1.3 | 42 | 45 | 3.3 | 2.7 | 0 | 0 |
| **Mean*** | **106.9** | **57.8** | **2.25** | **1.55** | **97.87** | **52.87** | **5.75** | **3.25** | **1.73** | **1** |

*Reference intervals: $TT_4$ = 10-55 nmol/L, $TT_3$ = 0.6-1.4 nmol/L, $fT_4ED$ = 10-50 pmol/L, $fT_3$ = 1.5-6.0 pmol/L, TSH = 0-21mU/L.*

**For mean calculations: $TT_4$ values >156, a value of 157 was used, $TT_3$ values >4.7, a value of 4.8 was used, and fT4ED values >128, a value of 129 was used.*

prepared for each sample collection time. A single-channel analyzer system attached to sodium iodide well crystal was used to determine radioactivity in each sample. The GFR was calculated from $^{99m}$Tc-DTPA plasma disappearance curves as previously described.[18]

**Statistical Analysis**

Analyses were performed using commercial software[j]. Descriptive statistics were presented as mean and standard deviation (SD). SCr concentration, GFR, and serum SDMA were compared using repeated measures ANOVA to analyze the difference between pre and post treatment effects. T-tests were used for evaluation of change over time. Significance was set at $p \leq 0.05$.

## RESULTS

Eighteen cats were initially evaluated, of which 15 met all inclusion criteria. Two cats were excluded due to refusal to eat the food, and another due to the owner's inability to ensure strict dietary compliance. One of the two cats that refused to eat the food and subsequently declined all types of diets, developed hepatic lipidosis, and was euthanized. Necropsy evaluation revealed diffuse, moderate to severe hepatic lipidosis, diffuse, severe pancreatic amyloidosis with interstitial fibrosis, and unilateral thyroid adenoma.

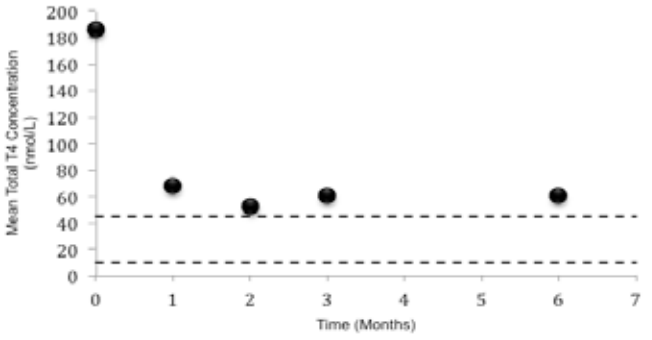
Thirteen cats were spayed females and two were castrated males with the median age 12 years old (range 7-16 years). The majority of cats were domestic short hairs (n=12), with one each of the following: domestic long hair, Maine Coon cat, and Siamese cross. All cats had an initial $TT_4$ concentration >56 nmol/L (reference interval 10-45 nmol/L) via CLEIA (Table 1) and > 49 nmol/L (reference interval 10-55 nmol/L) via MSU (Table 2). Results of the technetium thyroid scan (Table 3) revealed all cats had at least one thyroid to zygomatic salivary gland ratio of >1.2. Two cats had unilateral disease, 13 had bilateral disease, and no cats had ectopic thyroid tissue.

***Table 3.*** *Thyroid to zygomatic salivary gland ratios*

| Case No. | Right | Left |
|---|---|---|
| 1 | 11:1 | 39.7:1 |
| 2 | 19.4:1 | 5.7:1 |
| 3 | 3.78:1 | 1.43:1 |
| 4 | 5.66:1 | 1.88:1 |
| 5 | 45.75:1 | 17.04:1 |
| 6 | 47.23:1 | 2.99:1 |
| 7 | 2.19:1 | 6.08:1 |
| 8 | 0.84:1 | 4.39:1 |
| 9 | 2.33:1 | 10.45:1 |
| 10 | 5.19:1 | 33.26:1 |
| 11 | 7.45:1 | 4.2:1 |
| 12 | 3.24:1 | 4.02:1 |
| 13 | No uptake | 13.12:1 |
| 14 | 3.05:1 | 7.65:1 |
| 15 | 3.91:1 | 3.42:1 |
| **Mean** | **11.5:1** | **10.36:1** |

The mean body weight (kg), USG, UGGTC, ERD, SBP, EMD (left and right [cm]) and thyroid gland volume (mm3) at each evaluation are listed in Table 4. There was no difference found between any of these parameters

***Figure 1.*** *Mean $TT_4$ Concentration Overtime*




*Dashed lines represent the $TT_4$ concentration reference interval (10-45 nmol/L)*

***Table 4.*** *Variables evaluated before, 1, 3, and 6-months after treatment: body weight, USG, UGGTC, ERD, SBP, EMD and total thyroid volume*

| | Initial | 1-Month | 3-Month | 6-Month |
|---|---|---|---|---|
| Body weight (kg) | 4.13 (2.78-7.4) | 4.21 (2.83-7.12) | 4.23 (3.00-7.17) | 4.10 (2.97-6.76) |
| USG | 1.025 (1.012-1.051) | 1.027 (1.011-1.061) | 1.022 (1.008-1.061) | 1.024 (1.012-1.057) |
| UGGTC | 0.43 (0.2-1.3) | 0.29 (0.1-0.5) | 0.34 (0.1-0.8) | 0.30 (0.1-0.9) |
| ERD | 1 (0-2) | 0.8 (0-2) | 0.93 (0-2) | 0.67 (0-2) |
| SBP (mmHg) | 156 (125-190) | 155 (115-200) | 154 (120-190) | 156 (120-195) |
| Right EMD (cm)* | 1.55 (1.2-2.03) | n/a | n/a | 1.56 (1.07-2.15) |
| Left EMD (cm)* | 1.56 (1.2-2.01) | n/a | n/a | 1.62 (1.05-2.09) |
| Total Thyroid Volume (mm3)* | 369 | n/a | n/a | 281 |

*Data listed as mean and (range) values.*
*ERD values were scored as follows; negative = 0, low positive = 1, medium positive = 2, high positive = 3*
**Not all cats had all measurements available for EMD or thyroid gland volume calculations, the existing data was used in the analysis*

throughout the study period. Based on persistent hypertension on repeat blood pressure measurements, cats 1, 3, 4, and 15 were treated with amlodipine (average dose of 0.66 mg by mouth once daily). Mean values for CLEIA $TT_4$, GFR, SCr, SDMA, and UPC pre and post-treatment are listed in Table 5.

The mean serum CLEIA $TT_4$ concentration significantly decreased ($p < 0.001$) from a pretreatment value of 185.54 ± 138.0 nmol/L to a 6-month posttreatment value of 60.5 ± 35.5 nmol/L (reference interval 10-45 nmol/L) (Figure 1). Euthyroidism was achieved at study completion in 5 cats based on CLEIA results, and in 6 cats based on the MSU results.

There was a significant decrease in SCr concentration between the initial evaluation and 6-months post-treatment ($p < 0.001$) (Figure 2). No significant differences were observed between the initial and 6-month posttreatment GFR ($p = 0.71$), serum SDMA ($p = 0.41$), UPC ($p = 0.74$), or EMD ($p = 0.95$ and $p = 0.45$ for right and left EMD respectively) (Table 5).

## DISCUSSION

Feeding y/d Feline to hyperthyroid cats results in a significant decrease in circulating $TT_4$ concentration. Despite the significant decrease in $TT_4$, 9-10 of 15 cats had persistent $TT_4$ concentrations above the reference interval at the end of the study period. Persistent hyperthyroidism in these cats was most likely due to either poor patient or owner dietary compliance. Poor dietary compliance was documented in 24 of 68 cats fed y/d Feline in a previous study.[8] However, in the present study, no specific concerns about compliance were reported by owners at recheck evaluations.

In contrast to other treatment modalities,[2,4,5,19] management of hyperthyroidism with y/d Feline did not result in a decrease in GFR. Since hyperthyroidism is known to increase GFR, our lack of decline in GFR could be associated with persistent hyperthyroidism. However, to further investigate this potential, we compared the change in GFR values of the five euthyroid cats to the 10 that remained hyperthyroid at 6-months (CLEIA $TT_4$), and no change in GFR was

***Table 5.*** *Variables evaluated before and 6-months after treatment: CLEIA $TT_4$ concentration, GFR, SCr concentration, and serum SDMA concentration.*

| Case No. | $TT_4$ (nmol/L) | | GFR (ml/min/kg) | | SCr (mg/dl) | | SDMA (µg/dl) | | UPC | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Initial | 6 Months | Initial | 6 Months | Initial | 6 Months | Initial | 6 Months | Initial | 6 Months |
| 1 | 436 | 55 | 3.14 | 3.27 | 1.4 | 1.4 | 27 | 25 | 0.4 | 0.5 |
| 2 | 236 | 59 | 1.62 | 1.72 | 0.6 | 0.9 | 10 | 10 | 1.3 | 0.3 |
| 3 | 128 | 39.8 | 1.7 | 2.18 | 1.9 | 1.5 | 23 | 19 | 0.5 | 0.5 |
| 4 | 66.8 | 33.8 | 3.03 | 2 | 1.1 | 0.8 | 8 | 8 | 0.3 | 0.5 |
| 5 | 426 | 78.8 | 2.45 | 2.54 | 1.1 | 1.5 | 17 | 23 | 0.4 | 0.4 |
| 6 | 421 | 176 | 2.64 | 2.64 | 0.6 | 0.4 | 11 | 10 | 0.3 | 0.4 |
| 7 | 62.3 | 19.1 | 3.05 | 3.01 | 2 | 1.2 | 15 | 14 | 0.2 | 0.3 |
| 8 | 72.6 | 46.9 | 1.77 | 1.57 | 1.2 | 0.9 | 9 | 8 | 0.3 | 0.3 |
| 9 | 149 | 72.6 | 1.3 | 1.18 | 0.7 | 0.7 | 7 | 6 | 0.7 | 0.6 |
| 10 | 236 | 54.4 | 1.98 | 2.27 | 0.6 | 0.8 | 10 | 8 | 0.4 | 0.4 |
| 11 | 90.1 | 67.7 | 3.31 | 2.42 | 0.9 | 0.8 | 13 | 13 | 0.3 | 0.8 |
| 12 | 82 | 43.2 | 2.65 | 2.64 | 1.2 | 0.7 | 13 | 10 | 0.3 | 0.2 |
| 13 | 136 | 54 | n/a* | 2.13 | 1.1 | 0.8 | 9 | 9 | 0.4 | 0.3 |
| 14 | 185 | 64.2 | 1.86 | 1.61 | 1.1 | 0.7 | 6 | 9 | 0.1 | 0.2 |
| 15 | 56.3 | 43 | 1.9 | 2.7 | 1.1 | 0.9 | 9 | 12 | 0.2 | 0.2 |
| Mean | 185.5 | 60.5 | 2.31 | 2.26 | 1.10 | 0.93 | 12.46 | 12.26 | 0.41 | 0.39 |
| SD | 138.0 | 35.5 | 0.66 | 0.57 | 0.42 | 0.32 | 5.93 | 5.71 | 0.28 | 0.16 |
| p-value | | < 0.001 | | 0.71 | | < 0.05 | | 0.41 | | 0.74 |

*Reference intervals: $TT_4$ = 10-45 nmol/L; SCr = 0.8-2.1 mg/dl; serum SDMA <14 µg/dl; UPC <0.4*
**Initial GFR measurement for cat 13 was measured twice on two different occasions and each time found to be >10 ml/min/kg. This value is significantly higher than any published reference interval, and was therefore removed from the statistical analysis.*

observed in either group (p = 0.35). To further investigate our lack of decline in GFR as compared to previous studies evaluating the other treatment modalities, we compared the correlation between change in $TT_4$ and change in GFR. Previous studies[2,4,5] have shown a correlation between the decrease in $TT_4$ and a decline in GFR, whereas no correlation between change in $TT_4$ and GFR was observed in the present study (r = 0.25, p = 0.39). These data illustrate that regardless of a significant decline in $TT_4$, there was no decrease in GFR in the present study.

The lack of decline in GFR in the present study could also be associated with the fact that none of the cats had a $TT_4$ concentration below the reference interval. In dogs, it has been shown that GFR is negatively affected by hypothyroidism[20] and similar physiology is suspected in cats. Other treatment modalities,[2,4,5,19] have reported $TT_4$ concentrations below the reference interval in 25-79% of cats. Iatrogenic hypothyroidism, defined as a low serum $TT_4$ concentration and a high serum TSH concentration, has been reported in 20-48% of hyperthyroid cats receiving methimazole.[21,22] In both studies, cats with iatrogenic hypothyroidism were more likely to be azotemic compared with methimazole-treated cats with normal serum $TT_4$ and TSH concentrations.[21,22] Thyroid hormone supplementation in cats with iatrogenic hypothyroidism resulted in a significant decrease in SCr and resolution of the azotemia in 50% of cats.[23]

SCr concentration decreased (p < 0.001)

between initial evaluation and 6-months post-treatment. This is contrary to other treatment modalities,[2,5,19] but similar to other studies evaluating y/d Feline in client owned hyperthyroid cats.[8,9] Possible explanations for the decrease in SCr concentration include the lower content of heat-processed meat in y/d Feline as compared to other commercial cat foods. In people, increased amounts of heat-processed meats have been associated with increased serum creatinine,[24] presumably associated with increased creatinine absorption from the gastrointestinal tract, thus lower amounts of such meats in Hill's y/d may allow a decline in SCr. It is also possible that the omega-3 fatty acid supplemented diet had a reno-protective effect. In addition, a decrease in muscle mass was postulated as a potential cause for the decrease in SCr concentration in a previous study.[8] However, the present study showed no change in EMD, suggesting decreased muscle mass was less likely to be the cause for the decreased SCr concentration. It should be noted that although the decrease in SCr was statistically significant, it's unlikely that a change of < 0.2 mg/dl is clinically significant.

The left and right EMDs, as determined by ultrasonographic measurement, did not change over time in the present study. This lack of change may illustrate that many cats remained hyperthyroid and therefore did not gain muscle mass. In addition, a 6-month time frame may be insufficient to appreciate a change in EMD. The evaluation of epaxial muscle area has previously been shown more reliable than radiographic measurements of epaxial muscle height, and similarly reliable as CT, for the evaluation of overall muscle mass in aged dogs with sarcopenia.[25] It was suspected that the use of ultrasonographic measurement of the epaxial muscles in cats would provide similar information regarding overall muscle mass. Further studies are needed to specifically evaluate the use of EMD for the assessment of overall muscle mass in hyperthyroid cats.

Similar to GFR, SDMA concentrations did not change overtime. Previous studies of serum SDMA in cats demonstrated a linear correlation between serum SDMA and GFR,[12] and the present study found a similar correlation. Additionally, compared to SCr, serum SDMA was more highly correlated with GFR ($r = 0.71$ vs. $0.55$, $p = 0.04$). Thus, serum SDMA may be a better marker for GFR than SCr in hyperthyroid cats. Further study of serum SDMA in hyperthyroid cats is warranted.

There was no change in UPC, UGGTC or ERD observed throughout the study period. The lack of change in UPC is contrary to another report[19] in which there were significant decreases in UPC 4 weeks post $^{131}I$ treatment. This difference may be due to the low number of cats in our study that had UPCs > 0.4 pre-treatment, in comparison to the previously reported 85% of cats with pre-treatment proteinuria with UPC > 0.4.19 Lack of decline in ERD is similar to a previous study that found the urine albumin to creatinine ratio (UAC) did not decrease following successful treatment of hyperthyroidism.[26] The lack of decline in ERD in the present and the lack of decline in UAC in the previous study suggest that albuminuria is not a major contributor to the proteinuria observed in hyperthyroid cats.[26]

A major limitation of this study was the relatively small number of cats that were considered euthyroid at the end of the study period, effectively decreasing the sample size and making data interpretation more difficult. Every effort was taken to ensure that owners were adequately storing and administering the food, while ensuring the cats were not receiving any other source of nutrition, however 100% compliance was difficult to confirm. It is likely that unrecognized non-compliance contributed to the high percentage of cats that remained hyperthyroid. Although there was no difference found in the change in GFR vs. change in $TT_4$ in the euthyroid cats in the current study, confirmation of this finding is warranted with a larger sample of cats treated successfully for hyperthyroidism with a

controlled iodine diet.

## CONCLUSION

Feeding a controlled iodine diet for 6-months resulted in a significant decline in $TT_4$ concentration. However, 9-10 of the 15 cats had $TT_4$ above the reference interval. Compared with other treatment modalities for feline hyperthyroidism, feeding the iodine-controlled diet was associated with a significant decrease in SCr, and no change in GFR or EMD. In addition, SDMA was better correlated with GFR compared with SCr in hyperthyroid cats.

## FOOTNOTES

a. Immulite Chemiluminescent enzyme immunoassay, Siemens Healthcare, Erlangen, Germany.

b. Michigan State University Diagnostic Center, Lansing, MI.

c. Idexx Laboratories, Westbrook, Maine.

d. HESKA Corporation, Loveland, CO.

e. Ultrasonic Doppler Flow Detector, Parks Medical Electronics Inc, Aloha, OR.

f. Bili Labstix, Bayer Healthcare LLC., Morristown, NJ.

g Hitachi 911, Roche Diagnostics, Indianapolis, IN.

h Roche/Hitachi cobas c systems, Roche Diagnostics, Indianapolis, IN.

i. Ascend Laboratories, LLC, Montvale, NJ.

j. SAS, SAS Institute Inc, Cary, NC.

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## CONFLICT OF INTEREST

G. Grauer received a grant from Hill's Pet Nutrition to complete this study. No further conflicts of interest are reported.

## REFERENCES

1. Peterson ME. Spontaneous hyperthyroidism in the cat. *Am College Vet Intern Med*. 1979:108 (abstract).
2. Graves TK, Olivier NB, Nachreiner RF, et al. Changes in renal function associated with treatment of hyperthyroidism in cats. *Am J Vet Res* 1994;55:1745–1749.
3. Adams WH, Daniel GB, Legendre AM, et al. Changes in renal function in cats following treatment of hyperthyroidism using 131I. *Vet Radiol Ultrasound* 1997;38:231–238.
4. Becker TJ, Graves TK, Kruger JM, et al. Effects of methimazole on renal function in cats with hyperthyroidism. *J Am Anim Hosp Assoc* 2000; 36:215–223.
5. Boag AK, Neiger R, Slater L, et al. Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine. *Vet Rec* 2007; 161:711–715.
6. Melendez LD, Yamka RM, Forrester SD, et al. Titration of dietary iodine for reducing serum thyroxine concentrations in newly diagnosed hyperthyroid cats. *J Vet Intern Med* 2011; 25:683 (abstract).
7. Melendez LD, Yamka RM, Burris PA. Titration of dietary iodine for maintaining normal serum thyroxine concentrations in hyperthyroid cats. *J Vet Intern Med*. 2011;25:683 (abstract).
8. Van der Kooij M, Becvarova I, Meyer HP, et al. Effects of an iodine-restricted food on client-owned cats with hyperthyroidism. *J Feline Med Surg*. 2013; 16:491-498.
9. Hui TY, Bruyette DS, Moore GE, Scott-Moncrieff JC. Effect of feeding an iodine-restricted diet in cats with spontaneous hyperthyroidism. *J Vet Intern Med* 2015; 29:1063-1068.
10. Bode-Boger SM, Scalera F, Kielstein JT, et al. Symmetrical dimethylarginine: a new combined parameter for renal function and extent of coronary artery disease. *J Am Soc Nephrol*. 2006; 17:1128-1134.
11. Schwedhelm E, Rainer BH. The role of asymmetric and symmetric dimethylarginines in renal disease. *Nat Rev Nephrol*. 2011; 7:275-285.
12. Braff J, Obare M, Yerramilli J, et al. Relationship between serum symmetric dimethylarginine concentration and glomerular filtration rate in cats. *J Vet Intern Med* 2014; 28:1699–1701.
13. Hall JA, Yerramilli E, Obare M, et al. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Intern Med*. 2014; 28:1676-1683.
14. Wisner ER, Théon AP, Nyland TG, et al. Ultrasonographic examination of the thyroid gland of hyperthyroid cats: comparison to 99mTcO-4 scintigraphy. *Vet Radiol Ultrasound.* 1944; 1:53-58.
15. Beck KA, Hornof WJ, Feldman EC. The normal feline thyroid: technetium pertechnetate imaging and determination of thyroid to salivary gland radioactivity ratios in 10 normal cats. *Vet Radiol Ultrasound.* 1985;26(1):35-38.
16. Daniel GB, Sharp DS, Nieckarz JA. Quantitative thyroid scintigraphy as a predictor of serum thyroxin concentration in normal and hyperthyroid cats. V*et Radiol Ultrasound*. 2002; 43:374-382.
17. Barthez PY, Chew DJ, DiBartola SP. Simplified methods for estimation of 99mTc-Pentetate and 131I-Orthoiodohippurate plasma clearance in dogs and cats. *J Vet Intern Med* 2001; 15:200-208.
18. Twardock RA, Bahr A. Renal Scintigraphy. In:

Daniel GB, Berry CR, editors. Textbook of veterinary nuclear medicine. 2nd edition. American College of Veterinary Radiology; 2006: 330-336.

19. van Hoek I, Lefebvre HP, Peremans K, et al. Short- and long-term follow-up of glomerular and tubular renal markers of kidney function in hyperthyroid cats after treatment with radioiodine. *Domest Anim Endocrinol* 2009; 36:45–56.
20. Panciera DL, Lefebvre HP. Effect of experimental hypothyroidism on glomerular filtration rate and plasma creatinine concentration in dogs. *J Vet Intern Med* 2009; 23:1045-1050.
21. Aldridge C, Behrend EN, Martin LG, et al. Evaluation of thyroid-stimulating hormone, total thyroxine, and free thyroxine concentrations in hyperthyroid cats receiving methimazole treatment. *J Vet Intern Med* 2015; 29:862-868.
22. Williams TL, Elliott J, Syme HM. Association of iatrogenic hypothyroidism with azotemia and reduced survival time in cats treated for hyperthyroidism. *J Vet Intern Med* 2010; 24:1086-1092.
23. Williams, TL, Elliott J, Syme HM. Effect of renal function of restoration of euthyroidism in hyperthyroid cats with iatrogenic hypothyroidism. *J Vet Intern Med* 2014; 28:1251-1258.
24. Butani L, Polinsky MS, Kaiser BA, et al. Dietary protein intake significantly affects the serum creatinine concentration. *Kidney Int.* 2002; 61:1907.
25. Hutchinson D, Sutherland-Smith J, Watson AL, el al. Assessment of methods of evaluating sarcopenia in olds dogs. *Am J Vet Res*. 2012; 73:1794-1800.
26. Williams TL, Peak KJ, Brodbelt D, et al. Survival and the development of azotemia after treatment of hyperthyroid cats. *J Vet Intern Med* 2010; 24:863–869.