A Restricted Iodine Food Reduces Circulating Thyroxine Concentrations in Cats with Hyperthyroidism

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ABSTRACT

Hyperthyroidism is the most common endocrine disease in domestic cats. This study examined whether dietary iodine restriction can reduce thyroid hormone concentrations in hyperthyroid cats. We performed a 12-week randomized, blinded, prospective study in which hyperthyroid pet cats housed with their owners were fed a control food (n=15) or a prototype restricted iodine food (n=18). Elemental analysis confirmed that iodine levels were approximately 10-fold lower in the restricted iodine food than in the control food. In the restricted iodine group, serum total thyroxine (TT4), free thyroxine, triiodothyronine, creatinine, and alanine transaminase significantly decreased, while blood urea nitrogen, aspartate transaminase, and alkaline phosphatase did not significantly change. In contrast, in cats fed the control food, alanine transaminase and aspartate transaminase significantly increased, but none of the other measures changed. In the according-to-protocol cohort, at the end of the study, all 12 cats in the restricted iodine group had decreased TT4 concentrations, whereas in the control group, TT4 concentrations had decreased in four cats, increased in four, and not changed in two (p=0.0028). At the end of the study, 6 of 12 cats in the restricted iodine group and 0 of 10 in the control group were euthyroid (p=0.015). None of the cats in either group became hypothyroid, and body weights and urine specific gravity did not significantly change. These results show that over 12 weeks, feeding a restricted iodine food reduces serum thyroid hormone concentrations in hyperthyroid cats without negatively affecting other measures of health. Feeding a restricted iodine food warrants further study as a treatment option for feline hyperthyroidism.

INTRODUCTION

Hyperthyroidism is the most common endocrine disease in domestic cats, affecting approximately 2% of all cats (Edinboro et al., 2004). Common clinical signs of hyperthyroidism include weight loss, increased eating and drinking, vomiting, increased urination, behavioral changes, nervousness, poor grooming, and diarrhea (Thoday & Mooney, 1992). Untreated, hyperthyroidism can lead to thyrotoxic cardiomyopathy, which can result in heart failure. Unlike in humans, hyperthyroidism in cats shows no sex predisposition and the disease is not associated with the production of thyroid growth-stimulating antibodies (Peterson & Ward, 2007).

Current treatments for feline hyperthyroidism include surgery to remove all or part of the thyroid, ablation of thyroid tissue by radioiodine therapy, and anti-thyroid drugs such as methimazole (Trepanier, 2007). Although radioiodine is the preferred treatment, anti-thyroid drugs are commonly used. However, approximately one in five cats treated with methimazole suffer from side-effects, some of which may be serious (Peterson et al., 1988). Also, compliance and cost can be an issue with antithyroid medications because they must be administered daily.

Because iodine is essential for the production of thyroid hormones, we hypothesized that restricting iodine intake would decrease circulating thyroid hormone concentrations in hyperthyroid cats. We therefore performed a 12-week randomized, blinded study to compare the effects of a restricted iodine food and a control food on thyroid hormone concentrations in hyperthyroid cats. We also examined changes in serum chemistry, urine specific gravity, and body weight to assess the overall health of cats during treatment.

MATERIALS AND METHODS

Study Design

This was a 12-week prospective, randomized, blinded, controlled study evaluating a therapeutic food for the treatment of hyperthyroidism in pet cats. The study was conducted in the US between May 16 and September 19, 2003. The primary objective was to determine whether feeding a prototype restricted iodine food can reduce TT4 concentrations in cats with hyperthyroidism.

Ethical Treatment of Cats in the Study

All aspects of this trial were conducted in strict accordance with the Hill's Pet Nutrition, Inc. Global Animal Welfare Policy. The study protocol was reviewed and approved by Hill's Pet Nutrition's Institutional Animal Care and Use Committee. Owners provided written informed consent prior to enrollment of their pet in the study. Results of physical and clinical examinations were closely monitored by the primary care veterinarian and the sponsor's clinical research associates. Cats were dismissed from the study if they showed continued weight loss, an adverse event that warranted treatment or surgical intervention, or substantial progression of the hyperthyroid or other medical condition preventing study completion.

Cats

Pet cats suspected to be hyperthyroid on the basis of clinical observations were recruited from 39 veterinary hospitals in the U S. To be included in the study, cats had to be at least 10 years old and have a serum total thyroxine (TT4) concentration > 4.0 µg/dL. Exclusion criteria included the following:

- receiving anti-thyroid drug therapy or any drug that could affect circulating concentrations of thyroid hormones
- emaciated condition (ribs prominent and easily felt with no fat cover)
- ventroflexion of the neck
- marked muscular weakness
- respiratory distress
- systemic diseases
- fractious behavior
- pregnant or likely to become pregnant during the study
- receiving supplements containing iodine.

Permitted medications or supplements prescribed before the beginning of the study had to be continued at a constant dose during the study.

Study Conduct

Cats were randomized 1:1 to receive either a prototype restricted iodine food or a control food (Iams® Active Maturity™, P & G Pet Care, Mason, OH). Both foods were available in dry and wet formulations. All foods met or exceeded the complete and balanced nutrition guidelines of the Association of American Feed Control Officials for the maintenance of adult (>1-year-old) cats (with the exception of iodine levels in the restricted iodine food), and the restricted iodine foods satisfied the requirements of an adult feline maintenance food. Iodine levels in the food were measured by EpiBoron Instrumental Neutron Activation analysis at the University of Missouri-Columbia Research Reactor Center (Columbia, MO) (Spate et al., 1995). Nutritional content of the study foods was assessed using standard methods.

Owners were instructed to feed cats dry food, wet food, or a combination of the two according to their cat's preference and resting energy requirement, which was estimated as follows: kcal required = 70 × (body weight at enrollment in kg)$^{0.75}$. Cats were maintained in owners' homes during the course of the study. Both owners and investigators were blinded to which food they were offering the cats.

At weeks 0, 3, 6, and 12, cats were seen at veterinary clinics, where veterinarians performed physical examinations, measured body weight, collected urine samples for measurement of urine specific gravity, and collected blood samples for measurement of serum TT4, free thyroxine (FT4), and triiodothyronine (T3) concentrations, blood urea nitrogen (BUN) concentration, and serum activities of alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate aminotransferase (AST).

- Serum T3 and TT4 concentrations were measured by enzyme-linked immunosorbent assay and FT4 concentrations by equilibrium dialysis in conjunction with an enzyme-linked immunosorbent assay (Antech Diagnostic Laboratories, Lake Success, NY). Urine specific gravity was measured by refractometer. All other analytes were measured using standard methods at Antech Diagnostic Laboratories. Reference ranges were as follows:
- TT4, 0.8 – 4.0 μg/dL
- FT4, 10 –50 pmol/L
- T3, 40 – 150 ng/dL
- BUN, 14 – 36 mg/dL
- creatinine, 0.6 – 2.4 mg/dL
- ALP, 6 –102 IU/L
- ALT, 10 – 100 U/L
- AST, 10 – 100 U/L

All adverse events were recorded by investigators within 24 hr of their occurrence. The primary outcome measure for this study was the change from baseline (week 0) in serum TT4 concentration.

Statistical Analysis

All statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, NC). Primary efficacy analysis was performed in the according-to-protocol group, defined as all cats enrolled and completing the full 12 weeks of the study according to protocol. Safety is reported and sensitivity analysis was performed in the intent-to-treat group, defined as all cats enrolled in the study and fed study foods. Age, weight, and serum chemistry values at baseline were compared using a two-sample t-test. Sex and reproductive status was compared using Fisher's exact test, and body condition scores were compared using the Cochran-Mantel-Haenszel test. Changes in serum thyroid hormone and biochemical marker concentrations over time were examined for each food by analysis of variance using PROC MIXED.

AIC and BIC fit statistics were used to select the best covariance structure for each response variable. The Kenward-Rogers adjustment was used to adjust the standard errors and test statistics for the presence of correlated errors in the model. The time

Table 1. Nutritional analysis of the study foods

Component	Dry formulation		Wet formulation	
	Restricted iodine	Control	Restricted iodine	Control[a]
Iodine, ppm [range]	0.36 [0.27–0.60]	3.01	0.21 [0.14–0.27]	6.34
Protein, %	33.7	35.7	33.2	50.2
Fat, %	21.3	17.2	22.8	27.0
Carbohydrates (nitrogen-free extract), %	37.4	38.7	38.6	15.4
Crude fiber, %	2.4	1.7	1.8	0.4
Ash, %	5.1	6.7	5.0	6.9
kcal/kg	3830	4108	1073	1153

All values except for kcal/kg are on a dry-matter basis. For the control food, all values are for a single sample. For the restricted iodine food, 10 samples were taken at different times during production, and the value for iodine is the mean [range] of the 10 samples, while all other values are from a single determination using a mixture of the 10 samples.

main effect and food × time interaction effect were partitioned into linear and quadratic trends using orthogonal polynomials. Distributions of changes (increase/decrease/no change) and of euthyroid status were compared by Cochran-Mantel-Haenszel test. A p-value below 0.05 was considered to indicate a statistically significant difference.

RESULTS

Study Foods

Chemical analysis confirmed that the wet and dry formulations of the restricted iodine food had approximately 10-fold lower concentrations of iodine than the respective control foods (Table 1). Iodine levels in the dry and wet formulations, respectively, were 0.36 and 0.21 ppm in the restricted iodine food and 3.0 and 6.3 ppm in the control food. Nutritional contents were similar for the dry foods. For the wet foods, protein and fat were higher and carbohydrate and fiber lower in the control food than in the restricted iodine food.

Table 2. Disposition of cats included in the study

	Control food	Restricted iodine food
Enrolled	15	18
Developed concurrent medical condition precluding completion	1	2
Lack of compliance with study procedures	1	2
Worsening hyperthyroid condition	3	0
Died[a]	0	2
Completed the study according to protocol	10	12

[a] One cat died following anorexia, weight loss, dehydration, and poor hair coat quality associated with increased hepatic enzyme activities (ALT and ALP), and one cat died following diarrhea and surgery to repair a hernia.

Cats

Thirty-three cats were enrolled, including 18 that were started on the restricted iodine food and 15 on the control food (Table 2). Twelve cats on the restricted iodine food and 10 on the control food completed the study according to protocol. For the cats completing the study according to protocol, baseline age, sex, reproductive status, body weight, and body condition score were similar (Table 3).

Table 3. *Baseline demographics*

Characteristic	Control food (N=10)	Restricted iodine food (N=12)	P-value
Age at study start, years			
Mean ± standard deviation	13.4 ± 2.4	14.5 ± 2.2	0.28
Range	10 – 17	10 – 18	
Weight, kg			
Mean ± standard deviation	5.1 ± 1.7	3.9 ± 0.7	0.07
Range	2.3 – 8.1	2.8 – 5.4	
Body condition score			
Mean ± standard deviation	3.40 ± 0.97	2.75 ± 0.45	0.053
Range	2 – 5	2 – 3	
Sex, n (%)			
Female	8 (80)	6 (50)	0.20
Male	2 (20)	6 (50)	
Reproductive status, n (%)			
Neutered/spayed	10 (100)	11 (92)	1.00
Intact	0 (0)	1 (8)	

Values are for cats completing the study according to protocol. P-values between test and control groups were calculated using a two-sample t-test.

TT4

Cats fed the Restricted Iodine Food

In cats fed the prototype restricted iodine food, serum TT4 concentrations decreased significantly over time (Figure 1). The largest decrease in mean TT4 concentration occurred within 3 weeks. Compared to baseline, the mean TT4 concentration was 43% lower at week 3, 49% lower at week 6, and 44% lower at week 12. Euthyroid status, defined as a serum TT4 concentration between 0.8 and 4.0 μg/dL, was attained in 5 of 12 cats after 3 weeks and maintained until week 12. One additional cat attained euthyroid status at week 12. None of the cats had hypothyroxinemia at any time point, as defined by a TT4 concentration < 0.8 μg/dL. Serum TT4 concentrations also decreased in the intent-to-treat group (data not shown).

Cats Fed the Control Food

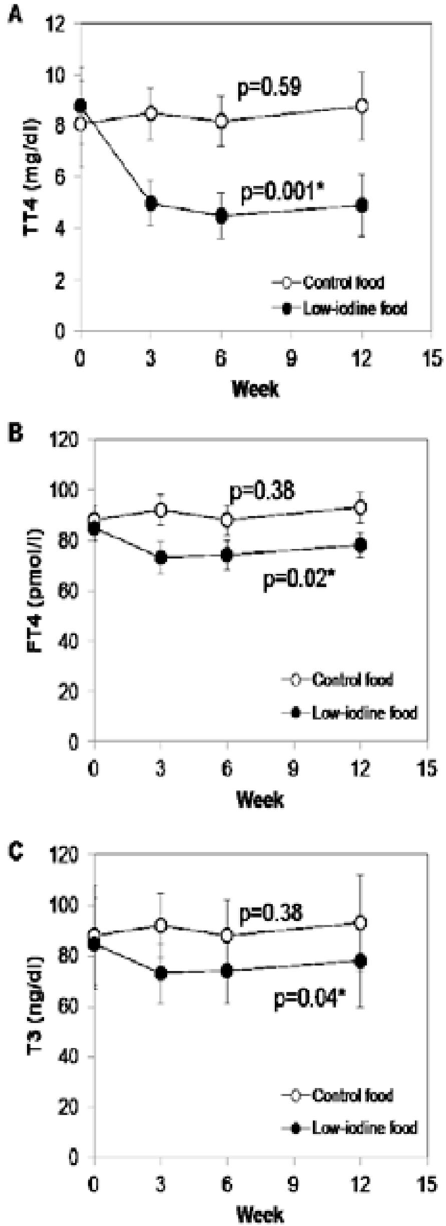
In cats fed the control food, serum TT4 concentrations did not significantly change over time (Figure 1). Compared to baseline, the mean TT4 concentration was 5% higher at week 3, 1% higher at week 6, and 9% higher at week 12. No cats fed the control food were euthyroid or hypothyroid at any time during the study. Results were similar in the intent-to-treat group, with no significant change in TT4 concentration over time (data not shown).

Comparison of TT4 Concentrations Between the Restricted Iodine and Control Groups

Changes in TT4 concentrations over time did not significantly differ between the restricted iodine and control groups (Figure 1). However, all 12 cats in the restricted iodine group had decreased TT4 concentrations, whereas in the control group, TT4 concentrations had decreased in four cats, increased in four, and not changed in two (p=0.0028). Moreover, the frequency of euthyroid status at the end of the study was significantly different between the restricted iodine and control group groups (6/12 vs. 0/10; p=0.0152).

Serum FT4 and T3 Concentrations

Figure 1. *Thyroid hormones Concentrations of (A) TT4, (B) FT4, and (C) T3 during the study. Values are means ± standard error for cats completing the study according to protocol. Best-fit P-values are shown. The best fit was linear except where marked with an asterisk (*), for which the best fit was quadratic.*



Serum FT4 and T3 concentrations changed significantly over time for cats fed the restricted iodine food (Figure 1). The largest decreases in mean FT4 and T3 concentrations occurred within 3 weeks. The serum concentrations of FT4 and T3 did not significantly change for cats fed the control food. Serum FT4 and T3 concentrations did not significantly change over time in the intent-to-treat groups (data not shown).

Serum Chemistry

For cats fed the restricted iodine food, serum creatinine and ALT decreased significantly, while BUN, ALP, and AST did not change (Figure 2). For cats fed the control food, serum ALT and AST increased significantly, while BUN, creatinine, and ALP did not significantly change. Results were similar for the 33 cats in the intent-to-treat group, although ALT activities did not change significantly in cats fed the restricted iodine food (data not shown).

Other Measures

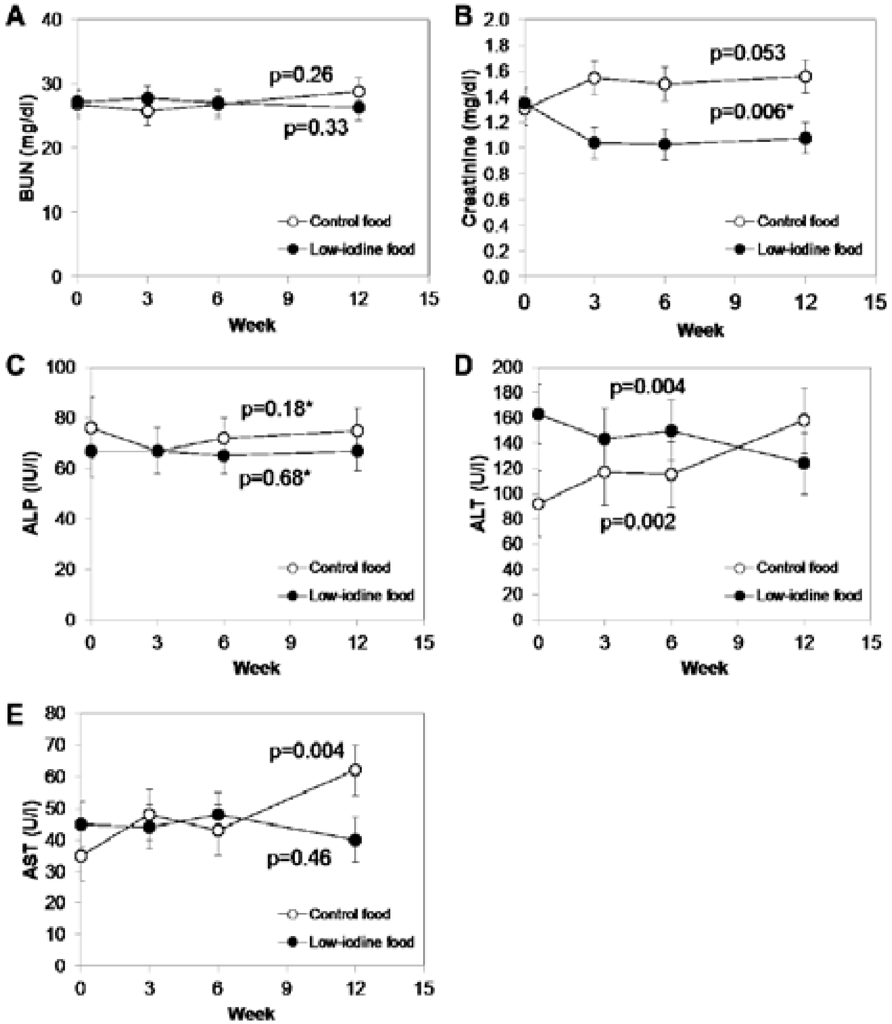
Mean body weights and urine specific gravity values did not significantly change over time in either group (data not shown).

Adverse Events

In the 33 cats originally enrolled in the study (intent-to-treat group), adverse events occurred in five cats fed the restricted iodine food and four cats fed the control food. For the control food, adverse events included:

- one cat with weight loss, muscle wasting, and loss of appetite, considered by the investigator to be due to worsening hyperthyroid condition
- one cat with weight loss, vomiting, and loss of appetite associated with pancreatitis
- one cat with increased TT4 and T3 concentrations from baseline, anorexia, tachycardia, grade 3-4 heart murmur considered by the investigator to be related to a worsening hyperthyroid condition
- one cat with increased vomiting, weight loss, and unkempt hair coat considered by the investigator to be

Figure 2. *Serum chemistry Concentrations of (A) BUN, (B) creatinine, (C) ALP, (D) ALT, and (E) AST during the study. Values are means ± standard error for cats completing the study according to protocol. Best-fit P-values are shown. The best fit was linear except where marked with an asterisk (*), for which the best fit was quadratic.*



related to a worsening hyperthyroid condition.

For the restricted iodine food, adverse events included:

- one with a fractured toe and associated abscess
- one cat with loss of appetite associated with a respiratory infection
- one cat that died following anorexia, weight loss, dehydration, and poor hair coat quality associated with increased hepatic enzyme activities (ALT and ALP)
- one cat that died following diarrhea and surgery to repair a hernia
- one cat that developed marked hyperglobulinemia.

DISCUSSION

This 12-week randomized, double-blinded, controlled study showed that feeding a prototype restricted iodine food rapidly reduces thyroid hormone concentrations in cats with hyperthyroidism. Treatment with the restricted iodine food appeared safe during the 12 weeks of the study.

Feeding the restricted iodine food resulted in a rapid and significant reduction in all thyroid hormone concentrations that was maintained until the end of the study. At the end of the study, all 12 cats in the restricted iodine group had decreased TT4 concentrations. Half of the cats fed the restricted iodine food attained euthyroid status, and in most, this was achieved within 3 weeks and maintained it until the end of the study. In the control group, in contrast, mean thyroid hormone concentrations did not significantly change and none of the cats attained euthyroid status at any time.

Dietary restriction of iodine with the restricted iodine food appeared safe during the 12 weeks of this study. Unlike the cats fed the control food, none of the cats fed the restricted iodine food had increased TT4 concentrations. Also, serum creatinine, BUN, AST, ALT levels, and urine specific gravity stayed the same or decreased in cats fed the restricted iodine food. Importantly, none of the cats fed the restricted iodine food became hypothyroid, and mean body weight did not change. A previous 12-month study in healthy adult cats also showed that a restricted iodine (0.17 ppm) food does not cause significant differences in body weight, food intake, serum chemistry, or complete blood count, and does not result in signs of iodine deficiency or goiter (Wedekind et al., 2009). Therefore, although the iodine levels in the prototype restricted iodine foods were below the National Research Council recommendations (1.4 ppm) (National Research Council, 2006), the studies to date suggest that these reduced levels are safe in both healthy and hyperthyroid cats, at least over a period of several months.

Serum creatinine concentrations have been shown to increase in hyperthyroid cats being treated with radioiodine, surgery, or methimazole (Adams et al., 1997; Becker et al., 2000; DiBartola et al., 1996; van Hoek et al., 2009). Unexpectedly, serum creatinine concentrations significantly decreased in cats fed the restricted iodine food. Decreased serum creatinine concentrations might indicate that the cats fed the restricted iodine food had improved renal function, although BUN concentrations and urine specific gravity did not change, and glomerular filtration rates would need to be measured to confirm this.

This study was 12 weeks long, which was sufficient to assess the acute effects of feeding a restricted iodine food. Despite including only 33 cats, this study was large enough to detect statistically and clinically significant improvements, most notably a 44% reduction in the mean TT4 concentration. Because the control and restricted iodine foods contained different ingredients, we cannot exclude the possibility that components other than iodine helped reduce TT4 concentrations. However, the restricted iodine food lowered TT4 concentrations in hyperthyroid cats not only compared to the control food but also compared to the start of the study, whereas TT4 concentrations did not significantly change with the control food.

The primary analyses were performed in the 22 cats completing the study according to protocol. TT4 concentrations were still significantly reduced in the restricted iodine group when the analysis was repeated in the full intent-to-treat group. Therefore, despite the early dismissal of 11 of these cats and their resulting exclusion from the principal analysis, the main results of this study appear robust. Interestingly, of the cats excluded from the according-to-protocol analysis, three, all in the control group, were discontinued early due to a worsening hyperthyroid condition.

Feline hyperthyroidism is currently treated by surgery, radioiodine therapy, and antithyroid drugs (Trepanier, 2007). Our results indicate that feeding a restricted iodine food may be an additional treatment option. We are currently performing additional studies to assess the long-term safety and efficacy of restricted iodine foods in treating feline hyperthyroidism.

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