Feline Hyperthyroidism - New Therapy (It’s in the Bowl!)
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Abstract:

Hyperthyroidism is now recognized as the most common endocrinopathy of older cats. Despite worldwide occurrence, the pathogenesis of feline hyperthyroidism remains unclear. Traditional methods of managing feline hyperthyroidism include thyroidectomy, anti-thyroid medications, and radioactive iodine. Surgery and radioactive iodine are designed to provide permanent solutions, oral anti-thyroid drugs are used to control hyperthyroidism and must be given daily to achieve and maintain their effect. All three modes of therapy are effective but none are without risks. Recent studies document that a fourth option now exists for hyperthyroid cats. Feeding a low-iodine food decreases thyroid hormone concentrations and alleviates clinical signs of hyperthyroidism in cats. Management of hyperthyroidism is now as safe and easy as feeding your cat.

Diagnosis:

Hyperthyroidism was first diagnosed in 1979 in the United States. Since it’s recognition in the late 1970’s the frequency of diagnosis has increased such that hyperthyroidism is now recognized worldwide as the most common endocrinopathy of older cats. A recent study in the UK suggests that 17% of the cats over nine years of age are diagnosed with hyperthyroidism each year. The incidence is similar in Australia, Germany, Japan and the United States. Interestingly, hyperthyroidism seems to be less common in some countries such as Spain and Hong Kong. Hyperthyroidism is generally considered a disease of middle-aged to older cats, with 12 to 13 years being the average age of onset. Less than 5% of cats are younger than 10 years of age at the time of diagnosis. Functional adenomatous hyperplasia of one (30%) or both (70%) thyroid lobes is the most common abnormality associated with feline hyperthyroidism. Typical clinical signs include weight loss with polyphagia, tachycardia, polyuria and polydipsia, nervousness or agitation, alopecia or unkempt haircoat, increased vocalization, heat intolerance and less often, vomiting, anorexia and lethargy. Most cats also have a palpable thyroid nodule. Diagnosis is generally based on the presence of one or more typical clinical signs and increased serum thyroxine (T₄) concentrations. However, up to 10% of all hyperthyroid cats and 40% of those with mild disease have serum T₄ values within reference range. Cats with mild or occult hyperthyroidism can be a diagnostic challenge. Random fluctuations of serum T₄ concentration into the normal range or a decrease in serum T₄ as a consequence of concurrent non-thyroidal illness (e.g., neoplasia, systemic infection, organ failure) can result in non-diagnostic total serum T₄ concentration in hyperthyroid cats. Therefore the diagnosis of hyperthyroidism should not be excluded on the basis of a single normal serum T₄ value, especially in a cat with typical clinical signs and a palpable thyroid nodule. In these cases, rule out concurrent non-thyroidal illness and repeat measurement of the total serum T₄ or evaluate simultaneous free T₄ and TSH measurements. An algorithm for diagnosing feline hyperthyroidism is included in Figure 1.
Risk Factors:

Despite the increasing worldwide prevalence, the pathogenesis of feline hyperthyroidism remains a mystery. A number of epidemiologic studies have attempted to elucidate causes for the apparent increased incidence of hyperthyroidism over the last 20 years.\(^{11-13}\) Although increased awareness, access to thyroid hormone assays and an increasingly aging cat population contribute to increased recognition, these factors may not completely explain the documented increase in prevalence of hyperthyroidism.\(^{11}\) It is likely that the underlying cause is multifactorial, with both genetic predispositions and environmental factors contributing to the manifestation of disease. Investigators have postulated that genetic, environmental (eg, toxins, goitrogens), and nutritional (eg, iodine) factors may play a role in the development of hyperthyroidism in cats.\(^{2,14-16}\)

Genetic Factors

Genetic contributions are supported by two studies that documented a significantly lower risk for hyperthyroidism in Siamese and Himalayan cats compared with other cat breeds.\(^{13,17}\) Investigators suggest that the apparent decreased prevalence of hyperthyroidism in mixed breed cats in Hong Kong may be in part the result of protective genetic factors since a large percentage of the domestic shorthaired cats in this geography are of oriental or Siamese descent.\(^{6}\)

Environmental Factors

Environmental exposures to a variety of substances have been evaluated in epidemiologic case controlled studies. Interestingly, the introduction of polybrominated diphenyl ethers (PBDEs) as flame-retardants into household materials nearly 30 years ago coincides with the timeline for increased incidence of feline hyperthyroidism.\(^{18}\) By the early 1980s, environmental levels of PBDEs had increased exponentially with commensurate increases in fish, waterfowl, and marine mammals. Although the main route of exposure for most persistent pollutants (eg PCBs and DDT) is through diet, it appears that inhalation of indoor air and dust is a more significant source of exposure to PBDEs.\(^{19,20}\) PBDEs can get into indoor air and dust after escaping from consumer products in the home such as furniture, carpets and appliances. In human medicine there is a growing concern over potential endocrine dysregulation secondary to PBDE exposure because of their structural similarity to thyroxine (T4) and toxicological effects in laboratory rodents and wildlife.\(^{18}\)

One study has hypothesized that the increases in feline hyperthyroidism observed worldwide are, in part, linked to parallel increases in the use of brominated flame retardants and that PBDE exposure of pet cats, similar to that of their owners, would likely occur through a combination of diet and contact with PBDE-containing household materials and dust.\(^{18}\) This study demonstrates that cats are being consistently exposed to PBDEs and this exposure may explain observed risk factors in other studies.\(^{18}\) The disproportionate increase in hyperthyroid cats in California correlates with that state’s aggressive legislation to decrease fire risk by requiring flame retardant materials in household items. Data on environmental contamination and increased levels of PBDE in ingredients commonly used in canned cat foods (fish, chicken livers) are also in good accord with the reported increased risk associated with consumption of canned foods. (Table 1) However since at least 25% of hyperthyroid cats reportedly never consume canned food, additional factors must be considered.\(^{11}\) Several studies have
documented indoor living\textsuperscript{11,12} or markers of indoor living (litter box use)\textsuperscript{17} as risk factors. These may simply be markers of increased exposure to PBDEs. The increased risk associated with indoor living is consistent with the data on PBDE content in house dust.\textsuperscript{19,20}

**Nutritional Factors**

Seven epidemiologic studies suggest that cats fed primarily (> 50%) canned food have an increased risk of developing hyperthyroidism.\textsuperscript{6,11-13,17,21,22} (Table 1) Cats exposed to a variety of flavors of canned food had an increased risk in one study\textsuperscript{12} while in two other studies cats who preferred specific flavors (fish or liver and giblet flavor) had a significantly increased risk of developing hyperthyroidism.\textsuperscript{21,22} While canned food was considered a risk factor for hyperthyroidism in a retrospective case controlled study of 379 hyperthyroid cats, this study also demonstrated a diminishing risk as the proportion of the diet that was commercial cat food increased. Additionally cats whose diet consisted of greater than 75% commercial dry food were at decreased risk for the disease.\textsuperscript{17} It is not clear if the decreased risk associated with commercial dry food consumption represents a protective effect of dry food or is related to a concomitant decrease in consumption of canned food by these cats.

Another factor implicated in the cause or progression of hyperthyroidism in cats is dietary iodine. The iodine content of commercial foods is highly variable and foods can be both deficient or in excess of recommended levels.\textsuperscript{23,24} These large variations in iodine content may reflect the highly variable iodine concentrations of ingredients used in these foods (eg organ tissue, fish). It is important to note that the most accurate method (i.e., neutron activation analysis) of measuring iodine in complex samples such as pet food was not used in these published studies. Traditional methods cannot detect iodine concentrations below 1 ppm. See *Measuring Iodine in Commercial Foods* for more information on determining iodine concentrations of commercial pet foods.

It has been suggested that wide swings in daily iodine intake may somehow contribute to the pathogenesis of hyperthyroidism in cats. One study suggests chronic iodine deficiency may be a risk factor since cats consuming commercial foods without iodine supplementation, according to listed ingredients, were more than four times as likely to develop hyperthyroidism compared with cats that ate iodine-supplemented foods.\textsuperscript{25} Three studies have evaluated the iodine content of commercial cat foods.\textsuperscript{23,24,26} Results of these studies document that between the 1980s and early 2000s commercial cat foods contained iodine concentrations that ranged from excessive (range 1.0 – 368 ppm iodine DMB) to non-detectable by traditional methods of measurement. To date, however, the presence of iodine deficiency or excess in the diet of hyperthyroid cats has not been documented. While serum-free T\textsubscript{4} concentrations have been shown to be acutely affected by varying dietary iodine intake, more prolonged ingestion (5 months) of either excessive or mildly deficient iodine foods had no apparent statistical effect on serum free thyroxine concentrations.\textsuperscript{27,28}

Proving a role of nutritional factors in feline hyperthyroidism is intriguing and parallels to the disease in humans are tempting. However the response to dietary iodine levels in people is not straightforward. Iodine deficiency in humans can cause both hypothyroidism and hyperthyroidism. Indeed, little is known about the optimum level of iodine intake for people, particularly with regard to iodine supplementation programs. Severe iodine deficiency is associated with an increase incidence of hypothyroidism in an affected population. Conversely,
mild to moderate iodine deficiency has been documented to increase the incidence of hyperthyroidism, particularly in elderly populations. In patients with mild to moderate iodine deficiency, the normal thyroid gland is able to adapt and keep thyroid hormone production within the normal range. However, the prolonged thyroid hyperactivity associated with this adaptation leads to thyroid hyperplasia. During follicular cell proliferation there is a tendency for mutations to occur which can lead to autonomous growth and function.

Excess iodine consumption can manifest as a variety of syndromes. Patients with chronic excess iodine consumption have been diagnosed with hypothyroidism and hyperthyroidism both with and without goiter, euthyroid goiter and occult or clinical autoimmune thyroid disease. Iodine induced hyperthyroidism (IIH) occurs most often, but not exclusively, in elderly members of chronically iodine deficient populations and in patients who have autonomous thyroid nodules. Typically the incidence of IIH spikes when these populations are exposed to an incremental increase in iodine intake often as a result of prophylactic programs designed to eradicate iodine deficiency. Historically the incidence of IIH is transient and peaks in the third to fifth year after introduction of iodine supplementation and will often disappear from the population once iodine intake has stabilized.

In addition to iodine, other goitrogenic compounds have been found in cat foods (Table 2). These may be of particular importance because most are metabolized by glucuronidation, a metabolic pathway particularly slow in the cat. Soybean is commonly used as a high quality vegetable protein in commercial cat foods and has been shown to have a goitrogenic effect in cats. While long term feeding studies have not been completed, short term administration of dietary soy to healthy cats resulted in a modest increase in serum T4 and free T4 concentrations relative to serum T3 concentrations. This effect has been attributed to an inhibitory effect of the soy isoflavones, genistein and diadzein, on thyroid peroxidase, an enzyme essential to thyroid hormone synthesis.

One epidemiologic study found cats that consumed pop-open canned food compared to cats that consumed dry food were at increased risk for hyperthyroidism. This finding led to the speculation that chemicals lining the cans, specifically bisphenol-A (BPA) may have leached into the food and served as a goitrogen. Bisphenol-A reduces binding of T3 to thyroid receptors and interferes with signal transduction in rats and has been detected in canned cat foods. It has been suggested that this proposed link between bisphenol-A and hyperthyroidism is tenuous. The potency of BPA is very low; a concentration of 200 µM is required for 50% displacement of T3 from thyroid hormone receptors. The reported range of concentration of BPA in cat foods is 13-136 ng/g of food. An average 11 lb cat consuming 100 g of food per day would consume a 3 µg/kg dose of BPA per day or about 1/30,000 of the dose shown to induce thyroid effects in rats (100mg/kg).

Summary

Clearly the underlying pathophysiology of feline hyperthyroidism remains an enigma. It is important to understand that while one aim of epidemiologic studies is to assess the cause of a disease most of these studies are observational which means a number of possible explanations for an observed association need to be considered before a cause – effect relationship can be said to exist. Observed associations may be due to chance (random error), bias (systematic error) or confounding conditions. Therefore an observed statistical association...
between a risk factor and a disease does not necessarily infer a causal relationship. The process of determining a cause-effect relationship is complex, and the inference of the nature of an association is a subjective process until prospective randomized trials can confirm the relationship.

**Nutritional Management: It’s in the bowl**

Excessive production of thyroid hormone is the hallmark of feline hyperthyroidism. Production of thyroid hormone requires uptake by the thyroid gland of sufficient amounts of iodine which is provided by dietary intake. It is not surprising that many metabolic pathways are upregulated in the thyroid glands of hyperthyroid cats. Indeed recent genomic studies have shown that the metabolic pathways responsible for transporting iodine into the thyroid cells and into the colloid for inclusion into thyroid hormones are considerably upregulated in hyperthyroid cats. This observation led to the question; if iodine transport systems are upregulated and dietary iodine is necessary for the production of thyroid hormones, what happens when dietary iodine is restricted in hyperthyroid cats? A therapeutic food, Hill’s Prescription Diet® y/d® Feline, was developed based on the hypothesis that feline hyperthyroidism can be managed nutritionally by limiting the amount of dietary iodine available for production of thyroid hormones. Prior to developing y/d Feline several technical challenges had to be overcome including accurately measuring very low levels of iodine in a complex substance (pet food) and developing a reliable manufacturing process to control the iodine content of finished product.

**Measuring Iodine in Commercial Foods:**

Iodine occurs naturally in many ingredients typically used in the manufacture of commercial pet foods, particularly fish, shellfish and fresh meats. (Table 3) Unless steps are taken to strictly control the iodine content of the ingredients, the final iodine concentration in pet foods will vary significantly and can be either high or low. Accurate measurement of iodine, particularly at low levels (below 1 ppm) in food has been a challenge due to complex matrix and the presence of potential interfering substances. A variety of techniques are used for the measurement of iodine in food including the Inductively Coupled Plasma Mass Spectroscopy (ICP-MS). ICP-MS methods are sensitive but yield recoveries that are erratic and frequently low due to loss of iodine in the sample extraction (digestion) step. Therefore products containing low levels of iodine, measured by traditional methods, and reported as having undetectable iodine content may in fact contain levels that are within the recommended range for a normal adult cat (0.46 ppm iodine DMB). Accurate measurements of iodine content of a complex matrix (such as pet food) can be achieved with Epiboron Neutron Activation Analysis (EBNAA). Epiboron Neutron activation analysis (EBNAA) is a sensitive analytical technique used for quantitative analysis of trace and rare elements. In EBNAA, the sample is placed in a nuclear reactor and is irradiated by stream of neutrons. The stable iodine is converted into an isotope of iodine, usually $^{128}$I. This isotope emits discrete gamma ray for iodine which is measured using a scintillation counter. In addition, EBNAA uses shielding techniques to eliminate interference from other elements present in food. EBNAA technique is unique and superior compared to other methods because of elimination of sample preparation step, high sensitivity and high specificity. For many elements including iodine, EBNAA offers sensitivities that are superior to those attainable by other
methods, on the order of parts per billion or better. In addition, because of its accuracy and reliability, EBNAA is generally recognized as the "referee method" of choice.\textsuperscript{57}

When comparing iodine levels in foods it is also important to consider how the iodine content is expressed; as fed or on a dry matter basis. The as fed basis ignores moister content which can make comparing foods problematic. Dry matter is that weight of food remaining after the water content is removed. This method accounts for the variability in water content between products. Dry matter basis is considered one of the most accurate methods of expressing nutrient content and is the only valid method for comparing nutrient content between dry and moist foods. Small differences in water content can significantly alter the DM content of nutrients. For example a dry and canned product from the same manufacturer labeled for the same lifestage (senior cats) may report 2.54 ppm and 0.8 ppm iodine respectively on an as fed basis. This would appear to suggest that the canned food has much less iodine than the dry product. Multiplying the nutrient content on an as fed basis by 4 for moist foods and adding 10% for dry foods is a shorthand method for converting as fed nutrient content to dry matter basis. Using this equation, the foods in the above example have \( \sim 2.8 \) ppm and 3.2 ppm iodine in the dry and canned varieties respectively. The canned variety actually contains more iodine than the dry product when expressed on dry matter basis.

*Manufacturing an Iodine- Restricted Food:*

Extreme care must be taken in the manufacturing process to assure a restricted iodine product reliably meets the target iodine concentration of \( \leq 0.32 \) ppm DMB. Cross contamination from ingredients stored and other foods manufactured in the same plant must be avoided. Commercial pet foods are manufactured using a batch system and multiple formulas are produced by the same machinery (line).\textsuperscript{41} (Figure 2) Normally ‘flushing’ the lines is an appropriate method of ensuring each product meets its unique nutrient specifications. However, ensuring the very low levels of iodine in y/d Feline requires more extensive precautions. Prior to manufacturing y/d Feline both dry and wet food manufacturing plants are closed for a complete, exhaustive cleaning. Once cleaned these lines are dedicated to producing y/d Feline for the duration of the ‘run’. Iodine levels of all ingredients are verified prior to inclusion in the food. Samples of the food are taken at various time points during each run and all finished food is tested to ensure it meets the iodine target prior to release.

*Clinical Studies Supporting Nutritional Management of Feline Hyperthyroidism:*

Three studies have documented the safety and efficacy of Hill’s Prescription Diet® y/d®Feline as the sole management in cats with naturally occurring hyperthyroidism.\textsuperscript{42-44} These studies were designed to determine the magnitude of iodine restriction necessary to return newly diagnosed cats to a euthyroid state\textsuperscript{43}; the maximum level of dietary iodine that will maintain cats in a euthyroid state\textsuperscript{42} and the efficacy of a therapeutic food formulated based on the previous studies to control naturally occurring hyperthyroidism in cats.\textsuperscript{44} The results of these studies support that a therapeutic food with dietary iodine levels at or below 0.32 ppm dry matter basis (DMB) provides an effective and safe therapy for cats with naturally occurring hyperthyroidism. Serum total thyroxine concentrations returned to the normal range within 8 to 12 weeks of initiating nutritional therapy in cats fed foods with \( \leq 0.32 \) ppm iodine DMB. All hyperthyroid cats maintained on foods with \( \leq 0.32 \) ppm iodine DMB as the sole source of
nutrition remained euthyroid. In all of these studies biochemical features of renal function remained stable and no other biochemical abnormalities were observed.

**Determining Iodine Requirements in Adult Cats**

To test the hypothesis that feline hyperthyroidism can be managed nutritionally by limiting the amount of dietary iodine available for production of thyroid hormones, first the minimum iodine requirement for an adult cat must be determined. Currently there is a discrepancy between AAFCO and NRC recommendations for minimum iodine requirements in adult cats. The National Research Council (2006) recently proposed that the nutrient allowance for iodine in adult cats is 1.4 ppm on dry matter basis (DMB) iodine in the diet. This recommendation is four times higher than the current AAFCO (2008) minimum recommendation (0.35 ppm iodine DMB) and is not in close agreement with the iodine requirement of other species. Neither of these recommendations is based on studies specifically and correctly designed to meet key criteria necessary for defining nutrient requirements. Based on the results of a study that was designed to meet the key criteria for nutrient requirements adult cats require a minimum of 0.46 ppm iodine (DMB). As expected this is in close agreement with other monogastric species such as dogs and humans. This estimate of minimum dietary iodine requirement is much lower than the proposed NRC 2006 recommended allowance for cats (1.4 ppm) but higher than the current AAFCO (2008) recommendation (0.35 ppm).

**Titration of Dietary Iodine in Newly Diagnosed Hyperthyroid Cats**

The next step in developing a nutritional solution to feline hyperthyroidism was to determine the iodine content of food necessary to return naïve hyperthyroid cats to the euthyroid state. To this end the initial titration study evaluated newly diagnosed hyperthyroid cats on three diets with progressively reduced iodine content (0.47 ppm DMB, 0.28 ppm DMB and 0.17 ppm DMB). Five domestic shorthair cats (8-17 years) were confirmed to have hyperthyroidism based on persistently increased serum total thyroxine concentrations (TT₄), palpable thyroid nodule and weight loss. Serum TT₄ concentrations ranged from 55-146 nmol/l (reference range 10–55 nmol/l). The cats were then first fed a low iodine containing food (0.47 ppm iodine DMB, as measured by epiboron neutron atomic activation). Serum TT₄ concentrations were measured every 3 weeks. Biochemistry parameters were also evaluated at weeks 0, 6 and 9. At 9 weeks, serum TT₄ concentrations had decreased in all cats with 4 of 5 cats (80%) being euthyroid (mean 48 nmol/l; range 41–54 nmol/l). The remaining hyperthyroid cat had an initial serum TT₄ of 146 nmol/l, which decreased to 83 nmol/l after being fed the low iodine food. The mean decrease in TT₄ for all 5 cats was 26 nmol/l (range 8–63 nmol/l). Renal parameters remained stable in all 5 cats.

In the second titration, these 5 cats along with 4 additional newly diagnosed hyperthyroid cats were transitioned to a food that contained less iodine (0.28 ppm DMB). Baseline serum TT₄ concentrations in the 4 new cats ranged from 55–73 nmol/l. Serum TT₄ and other biochemical parameters were monitored every 3 weeks for 9 weeks. While consuming the 0.28 ppm iodine food the four new cats became euthyroid with a mean TT₄ concentration of 41 nmol/ (range 29–50nmol/l). The 4 euthyroid cats from the earlier feeding study had further decreases in their TT₄ concentrations (mean TT₄=39 nmol/l, range 38–54nmol/l). The single non-euthyroid cat from the first study had a serum TT₄ concentration of 61 nmol/l, a
decrease from the baseline concentration of 83 nmol/l but still above the normal range. The average decrease in serum TT4 for all 9 cats was 20 nmol/l (range 2–35 nmol/l). After the end of this study one of these 9 cats was euthanized as a result of non-thyroidal illness. In the final titration, the remaining 8 of the original 9 cats along with one other newly diagnosed hyperthyroid cat (79 nmol/l serum TT4) were fed a third low iodine food (0.17 ppm DMB) and evaluated every 4 weeks for 12 weeks. All 9 of these cats were euthyroid (mean TT4= 33 nmol/l; range 23–50 nmol/l) by 12 weeks. This result included the cat whose serum TT4 remained in the hyperthyroid range in the first two titrations. The average decrease in TT4 was 13 nmol/l (range 0–43 nmol/l). Biochemical features of renal function remained stable and no other biochemical abnormalities were observed.

In summary, the results of this titration study demonstrate that feline hyperthyroidism can be managed effectively with a low iodine food.

**Titration of Dietary Iodine for Maintaining Normal Serum Thyroxine**

This study was designed to determine the maximum level of iodine in a nutritionally balanced feline mature adult food required to maintain normal serum TT4 concentrations in hyperthyroid cats currently being controlled on a food containing 0.17 ppm (DMB) as measured by epiborin neutron atomic activation.42 Eighteen cats previously diagnosed as hyperthyroid at least 14 months prior to the start of the study and whose TT4 concentrations had been maintained in the normal range by nutritional therapy with a low iodine food for a minimum of 10 months (range 10 months- 3 years) participated in the study. Serum TT4 concentrations ranged from 9–42 nmol/l (reference range 10–55 nmol/l) at the beginning of the study. The cats were divided into two groups each containing 9 cats. Groups were similar in age and gender distribution (mean age = 13.8 years, range 12–18 years). One group (Group A) was placed on a food that was formulated for mature adult cats containing 0.39 ppm iodine (DMB). The other group (Group B) was placed on a food that differed only in that it contained 0.47 ppm iodine (DMB). Blood was collected from all cats every three weeks and analyzed for serum TT4 concentration. Biochemistry parameters were also evaluated at weeks 0, 6 and 9.

All Group A cats exhibited increases in serum TT4 concentration (mean increase of 25 nmol/l above baseline, range 5–48 nmol/l). Seven of the cats remained in the euthyroid range (mean serum TT4 = 36 nmol/l, range- 27–54 nmol/l). Two cats exceeded the upper limit of the reference range (59 and 76 nmol/l respectively). The cats in Group B also exhibited increases in serum TT4 concentration but to a greater degree than the cats in Group A (mean increase 39 nmol/l, range 20–60nmol/l). Four cats remained in the euthyroid range (mean serum TT4 = 41, range 29–49 nmol/l). The five remaining cats all exceeded the upper limit of the reference range (mean serum TT4 = 76 nmol/l, range- 59–99 nmol/l). All cats returned to a euthyroid state within 1 month of being returned to a diet containing 0.17 ppm iodine (DMB). It was determined that serum TT4 concentrations are not ideally controlled in the normal range in hyperthyroid cats fed a food containing ≥ 0.39 ppm iodine (DMB).

**Nutritional Management of with Cats with Naturally Occurring Hyperthyroidism**

Previous studies have shown that limiting dietary iodine to or below 0.27 ppm DMB induces euthyroidism in cats with hyperthyroidism compared with a similar diet containing 0.42 ppm iodine DMB. The objective of this study was to test whether dietary iodine at 0.32 ppm DMB would induce euthyroidism in cats with naturally occurring hyperthyroidism. Fourteen
cats with hyperthyroidism confirmed by serum TT₄ and FT₄ measurements were stratified into two groups based on gender and age. One group (control: 4 males and 3 females, age ranged from 11 to 15 years) was given a positive control dry cat food (0.17 ppm iodine DMB) while the other group (test: 3 males and 4 females, age ranged from 12 to 17 years) was fed a commercial dry cat food (1.9 ppm iodine DMB) for at least 6 weeks before the study. At week 0 the control cats continued to receive the same food (0.17 ppm iodine DMB) while cats in the test group were given a test food (0.32 ppm iodine DMB) for an additional 12 weeks. All cats had free access to their food and deionized water during the study. Blood samples were collected during weeks 0, 3, 6, and 12 of the study.

The control cats maintained euthyroidism during the study. The test food significantly reduced serum TT₄ (72 ± 12, 43 ± 9*, 42 ± 9*, 40 ± 6* nmol/L in weeks 0, 3, 6 and 12, respectively; *: p < 0.05 compared with week 0, Dunnett’s t test). Serum FT₄ was also significantly reduced at the end of the study (17 ± 2 vs. 23 ± 2 pmol, week 12 vs. week 0; Dunnett’s t test, p < 0.05). Serum FT₃ was within the reference range (10–55 pmol/L) in cats in both groups. Serum TT₃, FT₃, and TSH were not affected by the test food and were within the reference ranges (TT₃: 0.6–1.4 nmol/L, FT₃: 1.5–6 pmol/L, and TSH: 0–21 mU/L) in cats of both groups during the study. This study demonstrates that dietary iodine at or below 0.32 ppm DMB provides an effective and safe therapy for cats with naturally occurring hyperthyroidism.

Implementing Nutritional Management of Feline Hyperthyroidism in Your Practice:

Nutritional management of feline hyperthyroidism is appropriate for newly diagnosed patients as well as those patients currently being managed with anti-thyroid medications or in patients with recurrence of hyperthyroidism post thyroidectomy. Theoretically, pretreating hyperthyroid cats with y/d Feline should increase the uptake of ¹³¹I and potentially decrease the dose necessary to achieve euthyroidism in radioactive iodine therapy. While the method of therapy is as easy as feeding your patients, as with any therapeutic regimen appropriate monitoring is necessary, especially in cats with concurrent diseases (eg, kidney disease).

Nutritional management of newly diagnosed patients

For a patient newly diagnosed or with recurrence of hyperthyroidism post thyroidectomy without other complications (hypertension, cardiac disease) Hill’s Prescription Diet® y/d®Feline is appropriate as the sole therapy. (Figure 3) Most cats require less than 7 days to transition from their current food to y/d Feline. Palatability and acceptance of this food are excellent. It is crucial that owners understand that success of this therapy depends on y/d Feline being the sole source of nutrition for their cat to the exclusion of treats or human foods. The first recheck evaluation should be scheduled 4 weeks after beginning the transition to y/d Feline or 3 weeks after y/d Feline becomes the sole food and should include physical examination, T4, BUN and serum creatinine and urine specific gravity. Clinical improvement including weight gain, improved haircoat and decreased tachycardia/cardiac murmur are often noted by the first evaluation. By 8 weeks more clinical improvement should occur and 85% of cats will be euthyroid. By 12 weeks all cats should have normal T₄ values. If values remain abnormal poor adherence to dietary therapy should be suspected and a thorough history as

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* Data on file Hill’s Pet Nutrition Inc.
Guidelines for Managing Cats with Persistent Hyperthyroidism should be obtained. Cats with evidence of hypertension or cardiac disease should be managed with appropriate therapies. Propranolol and atenolol are betablockers commonly used to symptomatically control tachycardia, polypnoea, hypertension, and hyperexcitability in hyperthyroid cats. They may be used in combination with nutritional therapy when rapid control of the clinical signs is desired. The concurrent use of anti-thyroid drugs is generally not necessary in cats with mild to moderate clinical signs. If severe clinical signs (emaciation, severe metabolic and cardiac dysfunction) are present and rapid reduction of serum thyroxine is desired anti-thyroid medications can be administered concurrently with the transition to y/d Feline. Monitoring in these cases is similar to the guidelines for transitioning hyperthyroid cats currently controlled with anti-thyroid medications (Figure 4) and should include serum T₄ concentrations every 4 weeks until the values are within normal limits. Once the patient is euthyroid and has been eating y/d Feline exclusively for at least 2 weeks the anti-thyroid medication dose should be decreased or discontinued. The decision to discontinue or decrease the dose should be based on the individual response. Anti-thyroid medication should be discontinued if serum T₄ concentrations are low normal to below the reference range. Routine recheck evaluations at 4 and 8 weeks after stabilization should include physical examination, T₄, serum chemistries (BUN and creatinine) and urine specific gravity.

**Transitioning from Anti-Thyroid Medications**

A general guideline for transitioning hyperthyroid cats currently controlled with anti-thyroid medications to y/d Feline is outlined in Figure 4. This is a general guideline which can be used to transition the majority of hyperthyroid cats from anti-thyroid drugs to y/d Feline. However, veterinarians should use their own clinical judgment and individualize treatment for their patients based on all factors, including T₄ concentration and the period of time needed to transition to y/d Feline. For example, if baseline T₄ is low (below the reference range), it would be appropriate to either decrease the anti-thyroid drug dose when the transition to y/d Feline begins (as noted in Figure 4) or discontinue drug therapy altogether. For cats with normal T₄, gradually decreasing the anti-thyroid drug dose will provide some control of T₄ while the cat is being transitioned to y/d Feline. Cats with a high T₄ (above the reference range) are not being adequately managed with current anti-thyroid therapy and decreasing the dose is unlikely to have a major impact. If transition to y/d Feline requires longer than 7-10 days, it may be reasonable to discontinue anti-thyroid drugs more gradually.

**Guidelines for Managing Cats with Persistent Hyperthyroidism**

To date all hyperthyroid cats managed with Hill’s Prescription Diet® y/d®Feline as the sole source of nutrition have become and remained euthyroid as long as the cat had no access to other sources of dietary iodine. Persistently increased T₄ should raise concerns of poor adherence to dietary recommendations. Maintaining y/d Feline as the sole source of nutrition can be challenging for some owners. Discovering the source of dietary iodine intake can be a challenge for the veterinary health care team. In keeping with the principles of client centered communications, owners should be questioned in an open-ended, non-threatening manner. Sources of dietary iodine that may alter the response to this therapy include treats, flavored or compounded medications, access to ‘people food’, consumption of wild caught prey, and
access to other pet foods. The iodine content of compounded medications is of particular concern since most use fish flavoring that is likely high in iodine. The iodine content of many over the counter supplements may not be known. Any supplement, treat, homeopathic/holistic therapy or food additive that is fish flavored or derived from ingredients from the sea (fish, shellfish, seaweed etc.) should be suspect and discontinued. Table 3 lists some common foods and ingredients that are high in iodine. Taking the time to collect a thorough history from the owner may help uncover the source of poor adherence to dietary therapy. Table 4 lists a series of questions, the rationale for each question and actions that can be taken to rule out sources of dietary iodine intake. Iodine content of water may be implicated if all other sources of iodine have been eliminated. This is unlikely if cats are supplied water from municipal water sources but possible if well water or natural sources of water are available. Consider switching to distilled water for one month to assess the response.

**Adverse Effects of Nutritional Therapy**

Based on the studies completed to date, no adverse effects of nutritional therapy have been noted. In all cats treated to date biochemical features of renal function have remained stable and no other biochemical abnormalities have been observed. There have been no reports of hypothyroidism or progression of kidney disease. Cats with IRIS stage 1 kidney disease have been managed with y/d Feline without progression of the disease. One hundred percent of hyperthyroid cats whose sole source of nutrition is y/d Feline have become euthyroid. Hypothyroidism has not been reported in cats managed exclusively with y/d Feline.

**Feeding Normal Cats Iodine Restricted Foods**

Hill’s Prescription Diet® y/d®Feline is not intended to be used as a maintenance food for healthy cats. However, often owners of multcat households prefer to offer dry food free choice to all their cats. While y/d Feline is contraindicated in growing kittens and reproducing queens its safety in adult cats has been evaluated. In a 6 month feeding trial eight normal cats (average age 4.6 years) were fed a restricted iodine food (0.22 ppm DMB) as the sole source of nutrition. Serum total thyroxine and total T3 decreased by 15-20% over the course of the study but like the biochemical parameters remained within normal limits. (Figure 5) Although not specifically designed to assess the safety of a low iodine food in normal cats, the process of determining the minimum requirements of iodine for adult cats does provide some information. In this study a group of 6 cats randomly assigned from a group of 42 adult cats (14 neutered males and 28 spayed females) ranging in age from 1.6–13.6 years (mean = 8.1 years) were fed a food formulated with 0.17 ppm iodine for 1 year. No physical examination abnormalities were noted and all biochemical parameters including TT4 were within normal limits for the duration of the study.

**Conclusion:**

Hyperthyroidism is common older cats. While the pathogenesis of feline hyperthyroidism remains unclear a variety of treatment options are available. Traditional

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b Data on file Hill’s Pet Nutrition, Inc.

methods of managing feline hyperthyroidism include thyroidectomy, anti-thyroid medications, and radioactive iodine. All three modes of therapy are effective but none are without risk of side effects. Hill’s Prescription Diet® y/d Feline® is the first therapeutic food specifically formulated to manage hyperthyroidism in cats. Studies document that when y/d Feline is the sole source of nutrition 100% of hyperthyroid cats return to and remain euthyroid. Management of hyperthyroidism is now as safe and easy as feeding your cat.

**Figure 1. Algorithm for Diagnosing Feline Hyperthyroidism**

*One option is to repeat T₄ measurement in 2-4 weeks*
Table 1. Summary of Epidemiologic Studies of Risk Factors for Feline Hyperthyroidism

<table>
<thead>
<tr>
<th>Study Reference / location</th>
<th>Number of cases (controls)</th>
<th>Study Dates</th>
<th>Diet studied</th>
<th>Reported Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarlett (1988)&lt;sup&gt;13&lt;/sup&gt; US</td>
<td>56 (117)</td>
<td>1982-1985</td>
<td>Diet for past 5 years</td>
<td>&gt;50% canned food, Indoor housing, exposure to lawn or flea control products, Non-Siamese breed</td>
</tr>
<tr>
<td>Kass (1999)&lt;sup&gt;17&lt;/sup&gt; US</td>
<td>379 (351)</td>
<td>1986</td>
<td>Current and 1 previous diet</td>
<td>&gt;50% canned food, exposure to cat litter, Non Siamese or Himalayan breeds</td>
</tr>
<tr>
<td>Martin (2000)&lt;sup&gt;21&lt;/sup&gt; US</td>
<td>100 (163)</td>
<td>1996-1997</td>
<td>Diet for past 5 years</td>
<td>Increasing age, preference for fish or liver &amp; giblet flavor canned foods</td>
</tr>
</tbody>
</table>
Table 2. Goitrogenic factors in foods and the environment*

<table>
<thead>
<tr>
<th>Nutrients or food types</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabbage (goitrin)</td>
<td>Polychlorinated biphenyls (fish-containing foods)</td>
</tr>
<tr>
<td>Canned foods</td>
<td>Pesticides</td>
</tr>
<tr>
<td>Cassava (linamarin)</td>
<td>Phthalates</td>
</tr>
<tr>
<td>Cyanides</td>
<td>Polyphenols (fish-containing foods)</td>
</tr>
<tr>
<td>Excess iodine</td>
<td>Propylthiouracil (drug)</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>Resorcinols (fish-containing foods)</td>
</tr>
<tr>
<td>Millet</td>
<td></td>
</tr>
<tr>
<td>Rutabagas</td>
<td></td>
</tr>
<tr>
<td>Sweet potatoes</td>
<td></td>
</tr>
<tr>
<td>Turnips</td>
<td></td>
</tr>
<tr>
<td>Seaweed</td>
<td></td>
</tr>
<tr>
<td>Various beans (including soybeans)</td>
<td></td>
</tr>
</tbody>
</table>

*Epidemiologic associations and risk factors.

Table 3. Foods and Ingredients with High Iodine

| Iodized salt, sea salt     |                                                   |
| All dairy products: milk, sour cream, cheese, cream, yogurt, butter, ice cream |                                                   |
| Margarine                  |                                                   |
| Egg yolks                  |                                                   |
| Seafood: fish, shellfish, seaweed, kelp |                                                   |
| Seaweed-based additives: carrageenan, agar-agar, algin, alginate, nori |                                                   |
| Prepared and/ or cured meats (ham, bacon, sausage, corned beef etc.) |                                                   |
| Fresh poultry with broth or additives injected |                                                   |
| Dried fruit                |                                                   |
| Canned vegetables          |                                                   |
| Commercial bakery products |                                                   |
| Molasses                   |                                                   |
| Soy product: soy sauce, soy milk, tofu |                                                   |
| E 127 Erythrosine: this appears in many foods or pills that are red or brown including colas |                                                   |
| Most chocolate (for milk content) |                                                   |
| Beans: red kidney beans, lima beans, navy beans, pinto bean and cowpeas |                                                   |
| Rhubarb and potato skins    |                                                   |
| Fresh meats (chicken, beef, lamb, pork and veal) most meat contains 25-130 mcg iodine per lb |                                                   |
| Rice and grains vary in the amount of iodine depending on the region where grown |                                                   |
Figure 2. Manufacturing Commercial Pet Foods

a) Steps used in manufacturing dry pet foods are similar to baking bread

b) Steps used in manufacturing canned foods
Figure 3. Algorithm for nutritional management of newly diagnosed hyperthyroid cats

*Most cats transition to the food over 7 days; some may need longer (several weeks).
†4 and 8 weeks after transition to y/d Feline is complete.
‡Cats with kidney disease should have rechecks at 2, 4, and 8 weeks after transition to y/d Feline is complete.
§Every 6 months indefinitely; cats with concurrent disease (eg, kidney disease) should be evaluated every 3-4 months.

$T_4$ should be decreased at first recheck and near or within reference range by second recheck. If not, see “Guidelines for Managing Cats with Persistent Hyperthyroidism.”
Figure 4. Algorithm for transitioning from anti-thyroid medications to nutritional management

1. **Begin gradual transition to y/d Feline* and decrease daily medication dose by 50%**

2. **Discontinue medication when cat has been eating y/d Feline exclusively for 1-2 weeks**

3. **Initial Recheck†**
   - Physical exam, T₄, BUN, serum creatinine, urine specific gravity

4. **Long-term Rechecks‡**
   - Physical exam, T₄, CBC, serum chemistries, UA

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*Most cats transition to the food over 7 days; however, some may need longer (several weeks).†At 4 and 8 weeks after transition to y/d Feline is complete. Cats with kidney disease should have rechecks at 2, 4, and 8 weeks after transition to y/d Feline is complete.‡Continue indefinitely; cats with concurrent diseases (eg, kidney disease) should be evaluated every 3-4 months.

These are general guidelines only – use clinical judgment to make decisions for individual patients (eg, if baseline T₄ is low, consider discontinuing medication).

T₄ should be decreased at first recheck and near or within reference range by second recheck. If not, see “Guidelines for Managing Cats with Persistent Hyperthyroidism.”
<table>
<thead>
<tr>
<th>Question</th>
<th>Rationale</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe how your cat spends its day.</td>
<td>Evaluate access to outside and to other sources of food. Cats with unsupervised access to outside may be ingesting neighbor’s pet food or wild caught prey.</td>
<td>Consider confining cats indoors for 1 month to assess efficacy of therapy.</td>
</tr>
<tr>
<td>How many other pets are in your house?</td>
<td>Evaluate access to other pet’s food (dogs, cats, birds, ‘pocket pets’ etc).</td>
<td>Hyperthyroid cats must not have access to other pets’ foods. Remove all food after feeding or confine the hyperthyroid cat to areas without access to other pets’ food.</td>
</tr>
<tr>
<td>What is your cat’s favorite food / treat?</td>
<td>Evaluate if cat is being offered foods other than y/d Feline. This is a nonthreatening way of finding out if owners are offering special treats or people food. Many owners don’t consider people food or treats as part of the ‘diet’ or know that they are not ‘supposed’ to give treats and therefore may not mention them.</td>
<td>Reinforce the fact that for this therapy to be successful y/d Feline must be the sole source of nutrition. Table 3 lists common foods and ingredients that are high in iodine.</td>
</tr>
<tr>
<td>What are you feeding your cat?</td>
<td>Evaluate what foods are being offered. The ‘correct’ answer is y/d Feline exclusively. It is appropriate to ask several questions related to what foods the cat may have access to.</td>
<td>Reinforce the fact that for this therapy to be successful y/d Feline must be the sole source of nutrition. Table 3 lists common foods and ingredients that are high in iodine.</td>
</tr>
<tr>
<td>How are you feeding your cat?</td>
<td>Allow owner to describe how they store, prepare and serve the food. Contamination with iodine can occur if y/d Feline is decanted and stored in containers or is served in bowls not thoroughly cleaned that have previously been used for maintenance foods.</td>
<td>y/d Feline is most appropriately stored in the original container (bag or can). If food is decanted into a storage container use a new container or one that has been thoroughly cleaned (dishwasher). Likewise the bowl / serving dish should be new or thoroughly cleaned and used exclusively for y/d Feline.</td>
</tr>
<tr>
<td>What medications or supplements are you giving your cat?</td>
<td>Allow owners to describe all medications and supplements.</td>
<td>Flavored or artificially colored medications and supplements or supplements with fish or shell fish ingredients can be sources of iodine.</td>
</tr>
<tr>
<td>Who feeds your cat?</td>
<td>Evaluate the possibility that members other of the family are inadvertently contaminating the feeding dish or are other foods.</td>
<td>Designate one person in the household to be responsible for feeding the hyperthyroid cat and cleaning the feeding dishes.</td>
</tr>
<tr>
<td>Do you have children living at home?</td>
<td>Evaluate the possibility that cats have access to foods dropped on the floor or left on counters or that children are offering ‘treats’ or other people food to the cat.</td>
<td>Reinforce the fact that for this therapy to be successful y/d Feline must be the sole source of nutrition. Remove cat from kitchen / dining area during meal times.</td>
</tr>
</tbody>
</table>

Table 4: Guidelines for Managing Cats with Persistent Hyperthyroidism
Figure 5. Serum TT\textsubscript{4} and T\textsubscript{3} in Healthy Cats\textsuperscript{†} on Iodine Restricted Food\textsuperscript{*}\textsuperscript{d}

\[ \text{Serum TT}_{4} \text{ nmol/l} \]

TT\textsubscript{4} Reference range: 10-55 nmol/l

\[ \text{Serum T}_{3} \text{ nmol/l} \]

T\textsubscript{3} Reference range: 0.6-1.4 nmol/l

\textsuperscript{†}n = 8 healthy cats (average age 4.6 years)

\textsuperscript{*}Iodine restricted food contained 0.2 ppm iodine DMB fed for 26 weeks (end)

\textsuperscript{d} Data on file. Hill’s Pet Nutrition, Inc.


