Nutritional Management of Feline Hyperthyroidism
Dr Jennifer Ervin BVSc (Hons) Technical Services Veterinarian
Hill’s Pet Nutrition Australia

Hyperthyroidism is recognised as the most common endocrinopathy of older cats¹, however, despite worldwide occurrence, the pathogenesis of feline hyperthyroidism remains unclear. A number of epidemiologic studies have identified risk factors, however; as yet, none have been shown to cause hyperthyroidism. Traditional methods of managing feline hyperthyroidism include thyroidectomy, anti-thyroid medications, and radioactive iodine. Surgery and radioactive iodine are designed to provide permanent solutions whilst oral and transdermal anti-thyroid drugs are used to control hyperthyroidism, and must be given daily to achieve and maintain their effect. A fourth management option is now available for hyperthyroid cats in Australia; Hill’s Prescription Diet™ y/d™ (abbreviated to y/d™).

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 intake², prompting the hypothesis that limiting dietary iodine intake could be used to control thyroid hormone production and help manage hyperthyroidism in cats. After more than a decade of research and development, a limited-iodine therapeutic food, Hill’s Prescription Diet™ y/d™ was developed as a management option for hyperthyroid cats.

How was this Food Developed?
Many metabolic pathways are up regulated in the thyroid glands of hyperthyroid cats. 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 also considerably up regulated in these cats.³ Besides the central role of iodine in thyroid physiology, other physiological actions of iodine are not recognised. If iodine transport systems are up regulated and dietary iodine is necessary for the production of thyroid hormones, what happens when dietary iodine is restricted in hyperthyroid cats?

Development of y/d™ was 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™ 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 ensure precise control over 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. 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.⁴,⁵ Accurate measurement of iodine, particularly at low levels (below 1 ppm) in food has been a challenge due to the complex matrix of the product and the presence of potential interfering substances. A variety of techniques is 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 step. Therefore, products containing low levels of iodine as 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).⁶
Accurate measurements of iodine content of a complex matrix, such as pet food, can be achieved with Epi boron Neutron Activation Analysis (EBNAA). 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 a stream of neutrons. The stable iodine is converted into an isotope of iodine, usually $^{128}$I. This isotope emits discrete gamma rays for iodine, measured using a scintillation counter, and uses shielding techniques to eliminate interference from other elements present in food. EBNAA is superior to other methods because of elimination of the 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. Because of its accuracy and reliability, EBNAA is generally recognised as the "referee method" of choice.

When comparing iodine levels in foods it is important to consider how the iodine content is expressed, that is, on an "as fed" or on a dry matter basis (DMB). The as fed basis ignores the moisture content of the food, which can make comparing foods with differing moisture contents problematic. Dry matter is that weight of food remaining after the water content is removed, and thus accounts for the variability in water content between products. DMB is considered to be 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.

**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 ≤ 0.3 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, with multiple formulas produced by the same machinery (line). Normally, ‘flushing’ the lines is an appropriate method of ensuring each product meets its unique nutrient specifications, however achieving the very low levels of iodine in y/d™ requires more extensive precautions. Prior to manufacturing y/d™, both dry and wet food manufacturing plants are closed for a complete, exhaustive cleaning. Once cleaned these lines are dedicated to producing y/d 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**

A recently published prospective, multi-centre, non-controlled, open-label study evaluated the effects of an iodine-restricted food (y/d™) on circulating total thyroxine (TT4) concentrations and clinical parameters in 225 client owned hyperthyroid cats from 139 veterinary clinics in 10 European countries. This study showed that eating an iodine-restricted food is a valuable management option, able to decrease plasma TT4 concentrations and improve clinical signs and quality of life in these cats after 4-8 weeks. In addition, there were no indications of a decrease in renal function (GFR), commonly seen after successful management of hyperthyroidism in cats using other treatment methods. Interestingly, no difference, in response to the iodine restricted food, was found between indoor versus outdoor cats, suggesting that the possible ingestion of other food or prey was not sufficient to negate the effectiveness of y/d™.

Another recently published study also documented the safety and efficacy of feeding a restricted iodine food to manage cats with naturally occurring hyperthyroidism. This was a 12 week randomised, blinded, prospective study in which hyperthyroid pet cats housed with their owners were fed a control food or a restricted iodine food. In the cats fed the restricted iodine food, serum TT4 concentrations decreased significantly over time without any negative effects on other measures of health.
Three earlier studies\textsuperscript{12-14}, presented at ACVIM in 2011, documented the magnitude of iodine restriction necessary to return newly diagnosed hyperthyroid cats to a euthyroid state\textsuperscript{12}; the maximum level of dietary iodine that will maintain cats in a euthyroid state\textsuperscript{13}; and the efficacy of a therapeutic food formulated based on the previous studies to control naturally occurring hyperthyroidism in cats\textsuperscript{14}. These studies indicate that a therapeutic food with dietary iodine levels at or below 0.32 ppm dry matter basis (DMB) is an effective and safe therapy. Serum total thyroxine concentrations returned to the normal range within 8 to 12 weeks of initiating nutritional therapy in cats fed foods with ≤ 0.32 ppm iodine DMB. All hyperthyroid cats maintained on foods with ≤ 0.32 ppm iodine DMB as the sole source of nutrition remained euthyroid. In all of these studies\textsuperscript{12-14} biochemical features of renal function in all cats remained stable and no other biochemical abnormalities were observed.

**Reasons to Consider Nutritional Management of Feline Hyperthyroidism**

**Owner Factors**

- Radioactive iodine not available or the owner does not desire this option
- Owner reluctant to have cat away during hospitalisation period for radioactive iodine
- Costs of radioactive iodine treatment or surgery are prohibitive for the owner
- Owner capable of feeding only limited-iodine food as the sole source of nutrition
- Owner cannot comply with giving medications (oral or transdermal)
- Delivering frequent medication has negative impact on the family-pet bond

**Patient Factors**

- The cat has had an adverse reaction to anti-thyroid drugs
- Irreversible management not appropriate (e.g., concerns about unmasking or worsening early to moderate kidney disease)
- Thyroidectomy not appropriate (e.g., high anaesthetic risk due to cardiac disease, bilateral disease with higher risk of parathyroid damage)
- Cat has early to moderate kidney disease and is not already eating a therapeutic renal food

**Nutritional Management of Newly Diagnosed Cats (No Concurrent Disease)**

After confirming the diagnosis and performing a thorough patient evaluation, all management options should be discussed with owners. If nutritional management is selected, gradual transition to y/d™ over at least 7 days is recommended. Gradual transition is still recommended to decrease side effects (inappetence, vomiting, diarrhoea, flatulence) that can occur with any food change. Some cats may benefit from a transition over several weeks. It is very important to counsel owners so they understand that success of nutritional management depends on the limited-iodine food being the sole source of nutrition. The first recheck evaluation should be done 4 weeks after completing the transition to y/d™ (i.e., once the cat has eaten y/d™ exclusively for 4 weeks) and as a minimum should include physical examination and measurement of T4, BUN, serum creatinine, and urine specific gravity. Cats should have decreased T4 concentrations compared with baseline and there will be those patients which return to normal by the 4-week evaluation. Clinical improvement, including weight gain, improved hair coat and decreased tachycardia/cardiac murmur, may also be noted by the first evaluation. Clinical signs should continue improving, and by the next re-evaluation at 8 weeks, most cats can be expected to be euthyroid. It is expected that some cats will require slightly longer and may need a further evaluation at 12 weeks. As per other management options, hyperthyroid cats on y/d™ will need ongoing veterinary monitoring.
Transitioning from Anti-Thyroid Drugs

Concurrent use of anti-thyroid drugs and feeding y/d™ is NOT recommended because of the potential for causing a rapid decrease in T4 concentration and hypothyroidism. If the veterinarian decides to transition a hyperthyroid cat from anti-thyroid drugs to a limited-iodine food, a baseline evaluation (history, physical examination, CBC, serum chemistries, urinalysis, and T4) should be done prior to beginning nutritional management. This is very important for identifying concurrent diseases and establishing a base from which to evaluate effectiveness/impact of nutritional management. It should not be assumed that cats receiving anti-thyroid drugs have normal T4 concentrations. Some cats that are well regulated with anti-thyroid drugs may experience a transient increase in T4 after switching to nutritional management (rarely associated with a recurrence of clinical signs), which usually resolves once the cat has been eating y/d™ as the sole source of nutrition for 1-2 months. Monitoring is indicated as described for newly diagnosed patients (with or without concurrent disease).

Nutritional Management of Hyperthyroid Cats with Concurrent Chronic Kidney Disease

Chronic kidney disease is the most common concurrent condition of hyperthyroid cats. Both diseases have increased prevalence in geriatric patients. Strong evidence supports the use of therapeutic renal foods, specifically Hill’s Prescription Diet™ k/d™ Feline, for the management of IRIS Stage 2 cats with chronic kidney disease. That said, if nutritional management for hyperthyroidism is desired in a patient with concurrent chronic kidney disease (IRIS Stage 1-3), y/d™ may be an appropriate choice, particularly compared to commonly available maintenance foods. When compared with typical feline foods, y/d™ Feline contains controlled amounts of phosphorus and sodium, high quality/highly digestible protein, and is supplemented with omega-3 fatty acids. Additional study is needed to better understand the effects of feeding y/d™ to hyperthyroid cats with concurrent kidney disease, and hyperthyroid cats with kidney disease should be monitored closely regardless of which option is selected for managing their hyperthyroidism.

Diabetes mellitus may also occur in cats with hyperthyroidism. Dietary therapy is a cornerstone of the management of type II diabetes in cats, and recent studies suggest foods that contain 5% to 26% of calories from carbohydrates help maintain glycaemic control. The percent of calories from carbohydrates in y/d™ (23% dry, 24% canned) falls within these guidelines. Certainly for any individual patient with multiple diseases the clinician must weigh the pros and cons of managing each disorder and decide which one has the greatest impact on longevity and quality of life. Additional information and recommendations for nutritional management of complicated clinical cases is available from the Hill’s Veterinary Consultation Service. This service provides free case management, nutritional counselling and product support for veterinary hospitals. The service can be reached at 1800 800 733 or by email through the www.hillsvet.com.au website.

Guidelines for Managing Cats with Persistent Hyperthyroidism

Hyperthyroid cats managed with y/d™ with persistently increased T4 should raise concerns of poor adherence to dietary recommendations. Maintaining y/d™ as the sole source of nutrition can be challenging for some owners, and discovering the source of dietary iodine intake can be challenging 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. Appendix 1 lists a series of questions, the rationale for each question, and actions that can be taken to rule out sources of dietary iodine intake. Sources of dietary iodine that may alter the response to this therapy include treats, flavoured or compounded medications, access to ‘people food’, consumption of milk, and access to other pet foods. The iodine content of compounded medications is of particular concern since most use fish flavouring that is likely to be 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 flavoured or derived from ingredients from the sea (fish, shellfish, seaweed etc) should be suspect and discontinued. Taking the time to collect a thorough history from the owner may help uncover the source of poor adherence to dietary therapy. Iodine content of water may be implicated if all other sources of iodine have been eliminated. This is unlikely if cats are supplied with water from municipal water sources but possible if well water or natural sources of water are available. Consider switching to distilled water for 1 month to assess the response.

Conclusion

Hyperthyroidism is considered the most common endocrine disease of older cats worldwide. While the pathogenesis of feline hyperthyroidism remains unclear, several effective management options are available. All options should be discussed with pet owners, including pros and cons, so that the most appropriate option can be selected for individual patients and their owners. Studies\textsuperscript{3,6-9} document that restricting the amount of dietary iodine effectively decreases the production of thyroid hormone resulting in normalisation of circulating T4 concentration. Hill’s Prescription Diet\textsuperscript{™} y/d\textsuperscript{™} is the first therapeutic food specifically formulated to carefully limit dietary iodine and when fed under veterinary supervision, as the sole source of nutrition, it is a safe and effective option for the management of feline hyperthyroidism.
### Appendix 1: Guidelines for managing cats with persistent hyperthyroidism

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<thead>
<tr>
<th>Question</th>
<th>Rationale</th>
<th>Action</th>
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<tr>
<td>Describe how your cat spends his or her day.</td>
<td>Evaluate access to outside and other sources of food. Cats with unsupervised access outdoors may be ingesting other foods.</td>
<td>Consider confining cats indoors for 1 month and then assess effectiveness of nutritional management.</td>
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<tr>
<td>How many other pets are in your house?</td>
<td>Evaluate access to other pets’ food (dogs, cats, birds, ‘pocket pets’, etc.).</td>
<td>Remove all food after feeding or confine the hyperthyroid cat to areas without access to other pets’ food and reassess after 1 month.</td>
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<td>What is your cat’s favorite food or treat?</td>
<td>This is a nonthreatening way of determining if the cat is being offered treats or other food. Many owners don’t consider people food or treats as part of the ‘diet’ or they may not mention them.</td>
<td>Reinforce that Hill’s® Prescription Diet® y/d™ Feline must be the sole source of nutrition. Some high-iodine foods include dairy products, egg yolks, seafood, dried fruit, canned vegetables, cured meats, fresh chicken or turkey (with broth or additives injected), soy products, seaweed products (carrageen, alginate), and red dye #3 or E 127 erythrosine (found in many foods/pills that are red or brown color).</td>
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<td>What foods are offered to your cat?</td>
<td>Evaluate what foods are being offered and ask questions to determine what other foods are accessible to the patient.</td>
<td>Reinforce that y/d Feline must be the sole source of nutrition. See above for a list of common foods and ingredients that may be high in iodine.</td>
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<td>How is your cat fed?</td>
<td>Allow owners 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 other foods.</td>
<td>Recommend storing y/d Feline in the original bag or can. If food is decanted into a storage container, it should be new or thoroughly cleaned (dishwasher). Likewise, the bowl/serving dish should be new or thoroughly cleaned and used only for y/d Feline.</td>
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<tr>
<td>What medications or supplements are given to your cat?</td>
<td>Allow owners to describe all medications and supplements.</td>
<td>Flavored or artificially colored medications or supplements with fish or shell fish ingredients, and liquids used by compounding pharmacies can be sources of iodine.</td>
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<td>Who feeds your cat?</td>
<td>Evaluate the possibility that other members of the family are inadvertently contaminating the feeding dish or giving other foods.</td>
<td>Designate one person in the household to be responsible for feeding the hyperthyroid cat and cleaning the feeding dishes.</td>
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<tr>
<td>Do you have children living at home?</td>
<td>It’s possible for cats to consume foods dropped on the floor, left on counters or offered as treats (when parents aren’t watching).</td>
<td>Reinforce that y/d Feline must be the sole source of nutrition. See above for a list of common foods and ingredients that are high in iodine.</td>
</tr>
<tr>
<td>What is the cat’s water source?</td>
<td>Most municipal water sources contain minute amounts of iodine; however, other sources (e.g., well water, ponds) may contain more.</td>
<td>Consider switching to distilled water for 1 month and then re-evaluate effectiveness of nutritional management.</td>
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References