Diagnosis and management of feline hyperthyroidism: current perspectives

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Abstract: Previous and ongoing research has provided insights to the pathophysiology and diagnosis of hyperthyroidism as well as new treatment modalities. This paper reviews the etiology, clinical presentation, and clinicopathologic changes associated with hyperthyroidism, and provides a thorough explanation of confirmatory testing and treatment options.

Keywords: feline hyperthyroidism, diagnosis, management

Introduction

The clinical condition of feline hyperthyroidism occurs due to excessive production and secretion of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). It was first described in humans in 1913 and in cats in 1979.[1] In cats, hyperthyroidism is almost always a primary autonomous condition of one or both thyroid glands, with most cats (70%) having benign adenomatous disease of both glands,[2] and a minority (<5%) having malignant thyroid carcinoma.[3,4]

Etiology

The etiology of feline hyperthyroidism remains incompletely understood. Due to the increasing prevalence of hyperthyroidism since the syndrome was first identified in cats, the possible contributions of immunologic, nutritional, environmental, and genetic factors have been extensively evaluated. In human beings, hyperthyroidism is typically associated with autoimmune (Graves') disease, and a similar etiology has been investigated in cats. Although some hyperthyroid cats have been found to have autoantibodies mimicking thyroid-stimulating hormone (TSH) that may contribute to the development of hyperthyroidism,[5] other investigators have not been able to verify this finding.[6,7] Other studies have suggested an increased incidence of hyperthyroidism in cats fed mostly canned food, or specifically canned foods with fish or liver and giblet flavors.[8–11] Environmental factors that have been implicated include soy isoflavones, phthalates, resorcinol, polyphenols, and polychlorinated biphenyls, some of which are considered goitrogens and others that can be found in the environment or commercial cat foods.[12,13] Additionally, cats that are kept primarily indoors, and those that have regular exposure to flea sprays, fertilizers, pesticides, or insecticides, have been found to have an increased prevalence of hyperthyroidism, while Siamese, Himalayan, and purebred cats have been reported to have a decreased risk for hyperthyroidism.[8,11,12] A direct cause and effect between the above factors and the development of hyperthyroidism remains difficult to prove.

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Clinical presentation

Cats affected by hyperthyroidism have a mean age of 12–13 years, with less than 5% being younger than 10 years of age.[14] The diagnosis of feline hyperthyroidism involves consideration of clinical signs, physical examination findings, as well as clinicopathologic changes and specific confirmatory testing. Because thyroid hormones have multiple functions throughout the body, almost every organ system is affected by elevated thyroid hormone concentrations. Cats with clinical evidence of thyrotoxicosis typically have a history of weight loss in the face of a normal or increased appetite, increased activity/restlessness, polyuria/polydipsia, an unkempt coat, and gastrointestinal signs, such as vomiting and diarrhea.[2,4,14–16] However the severity of these signs has decreased in the past 20 years because the syndrome is recognized earlier in the course of disease, presumably due to increased awareness.[2,14–16] In addition, approximately 10% of affected cats exhibit so-called "apathetic hyperthyroidism", which is characterized by decreased appetite and lethargy.[2,15] More than 90% of hyperthyroid cats have a palpable thyroid nodule at the time of diagnosis. An elevation in thyroid hormone concentration also causes alterations in cardiovascular hemodynamics, affecting heart rate, heart rhythm, and cardiac output.[16–18] In hyperthyroid cats, this can be appreciated clinically by the presence of tachycardia, increased intensity of the heart beat, and arrhythmias, as well as a systolic heart murmur (usually grade I–III/VI), which occurs in approximately 50% of hyperthyroid cats.[2,14,15] Although these may be common findings on physical examination, congestive heart failure occurs infrequently.[2,14] Finally, mild to moderate hypertension was originally thought to be a common finding in hyperthyroid cats, which would resolve with return to a euthyroid state. Current reports indicate that approximately 10% of cats have hypertension at the time of diagnosis of hyperthyroidism,[19] and this is associated with a reduced survival time in hyperthyroid cats.[20] A further 20% of cats develop hypertension following treatment and return to a euthyroid state, which may be associated with the unmasking of renal dysfunction.[16,19,21]

Hematologic and biochemical abnormalities are common with hyperthyroidism. Approximately 40%–50% of cats with hyperthyroidism show slight elevations of packed cell volume, and approximately 20% develop a macrocytosis.[2,14] Erythrocyte changes are thought to result from an increased production of erythropoietin secondary to the increase in oxygen consumption that occurs in hyperthyroidism, as well as a direct effect on the bone marrow of thyroid hormone-mediated β-adrenergic stimulation to increase production and release of red blood cells.[22] Common leukogram changes include neutrophilia, lymphopenia, eosinopenia, and monocytosis.[14,15] The most common biochemical changes observed in hyperthyroid cats are increased aminotransferase (ALT) and alkaline phosphatase (ALP) levels. In fact, more than 90% of hyperthyroid cats have an elevation in either ALT or ALP.[2,4,14,15] Although elevations in ALT and/or ALP are typically mild, severe elevations can be observed. There are few data regarding the mechanism for liver enzyme elevation in cats with hyperthyroidism; however, in hyperthyroid rats, a direct toxic effect of T_3 resulting in lipid peroxidation, protein oxidation, and glutathione depletion of hepatic mitochondria with subsequent apoptosis has been observed.[23,24] Limited feline studies have shown that both liver and bone ALP isoenzymes contribute to serum ALP elevation in hyperthyroid cats.[25–27] Although previous recommendations included evaluating hyperthyroid cats with ALP or ALT activity >500 IU/L for concurrent disease,[2,14,15] further experience has revealed that the changes seen in the liver secondary to hyperthyroidism usually do not affect liver function testing, such as paired serum bile acids, so such testing may not be warranted.[28] In addition, histologic evaluation of the liver in cats with hyperthyroidism reveals nonspecific and mild changes,[4] and liver enzyme changes associated with hyperthyroidism usually return to within the reference interval with successful management of the disease.[29]

Urinalysis results in hyperthyroid cats are generally nonspecific; however, many hyperthyroid cats have mild proteinuria. Although the mechanism of proteinuria in hyperthyroid cats is incompletely understood, successful treatment of hyperthyroidism leads to a rapid decrease in urinary protein excretion as assessed by the urine protein to creatinine ratio and urine albumin to creatinine ratio.[30–32] It has also been reported that up to 12%–22% of hyperthyroid cats present with urinary tract infections.[33,34] When signalment, history, clinical signs, physical examination findings, and initial blood screenings are compatible with feline hyperthyroidism, additional confirmatory testing is recommended.

Specific thyroid function tests
Total T$_4$ concentration

Although T_3 is the biologically active form of thyroid hormone, T_4 is the primary hormone secreted from the thyroid gland and found in the circulation, and is later metabolized to T_3 in peripheral tissues.[35,36] Although total T_4 concentrations vary considerably throughout the day in cats with hyperthyroidism, more than 90% of hyperthyroid cats will be confirmed via random serum total T_4 testing.[4,37,38] In contrast, over 25% of hyperthyroid cats will have a serum

total T_3 within the reference interval.[14,37] Thus, circulating serum total T_4 is superior to serum total T_3 in identifying cats with hyperthyroidism, and is the initial screening test of choice.[14,39,40] Further, simultaneous measurement of total T_3 and total T_4 concentrations does not offer a diagnostic advantage over total T_4 measurement alone.[14,37,40]

Serum total T_4 concentration measures the protein-bound fraction and free hormone fractions. T_4 is highly protein-bound and the free (unbound) fraction makes up less than 1% of the circulating pool. Radioimmunoassay is the gold standard method for measurement of serum total T_4, but methodologic limitations associated with radioimmunoassay have prompted validation of other assay methods, including a homogeneous enzyme immunoassay and chemiluminescent enzyme immunoassay.[37,41–44] The availability of these methods varies with the laboratory used. In addition, a commercial semiquantitative enzyme-linked immunosorbent assay (ELISA) T_4 kit is available for in-house use. The ELISA method has the advantage of providing rapid results to the practitioner, and is accurate when compared with the radioimmunoassay method.[43] Overall, each of these tests has pros and cons, and the test chosen should be based on the turnaround time needed and test availability.

The total T_4 concentration in cats with early or mild hyperthyroidism may fall within the reference interval due to normal fluctuations of thyroid hormones in the circulation. Further, certain drugs and nonthyroid disorders can suppress total thyroid hormone concentrations. The mechanisms for this include altered thyroid hormone metabolism, altered T_4 binding within cells or with plasma carrier proteins, and altered transport of T_4 into cells.[45] Of hyperthyroid cats with a total T_4 concentration within the reference interval, approximately 20%–30% have concurrent illness and the remaining 70%–80% likely have early disease.[37] Thus, if a single random serum total T_4 value is within the reference interval in a cat with historical, physical examination, and laboratory changes compatible with hyperthyroidism, the total T_4 concentration should be determined several weeks later, in addition to ruling out and/or treating any nonthyroid illness.[41] If nonthyroid illness has been ruled out and a repeat total T_4 remains within the reference interval, performing a serum free T_4 assay is recommended.

Free T_4 concentration

Serum free T_4, the unbound fraction of T_4 hormone, represents less than 1% of total circulating thyroid hormone. Free T_4 is the only T_4 fraction that can diffuse across cell membranes, and serves as a "prohormone" for T_3.[36] Serum free T_4 is

a more sensitive test for hyperthyroidism than the serum total T_4. More than 95% of hyperthyroid cats with a total T_4 concentration within the reference interval will have an elevated free T_4 concentration.[37] It is generally accepted that cats with a total T_4 value in the upper third of the reference interval, an elevated free T_4 concentration, and compatible clinical signs, are likely hyperthyroid.[44] Because free T_4 is the only fraction able to diffuse across cell membranes, it is also the fraction that causes thyrotoxicosis. The free T_4 level is also affected by nonthyroid factors. Up to 12% of euthyroid cats may have an elevated free T_4 concentration due to nonthyroid illness, making measurement of free T_4 less specific for diagnosis of hyperthyroidism than total T_4.[37,45,46] For this reason, free T_4 should not be used as the sole diagnostic test for hyperthyroidism. The etiology underlying elevation of circulating free T_4 in nonthyroid disease is not completely known, but has been speculated to be due to impaired clearance of free T_4 from the serum.[35] Finally, hyperthyroid cats with an elevated total T_4 concentration will always have a concurrent elevation in free T_4 concentration. Therefore, measurement of free T_4 is not indicated or necessary if the total T_4 is elevated.[37] If total T_4 and free T_4 concentrations are found within the reference interval on several separate occasions, but clinical suspicion of hyperthyroidism remains high, additional testing, with, eg, a T_3 suppression test, thyrotropin-releasing hormone (TRH) stimulation test, TSH response test, or thyroid scintigraphy should be considered.

T_3 suppression test

The T_3 suppression test evaluates the integrity of the physiological feedback loop via which thyroid hormone regulates pituitary gland function. In normal cats, thyroid hormone exerts negative feedback on the hypothalamus and anterior pituitary, and leads to decreased secretion of TRH and TSH, respectively, until inhibition is released by a fall in circulating thyroid hormone concentrations. The T_3 suppression test works according to the principle that administration of exogenous T_3 to a cat with normal thyroid function suppresses pituitary TSH secretion and leads to a decrease in endogenous T_4 secretion. Cats with primary hyperthyroidism, however, secrete thyroid hormones independent of pituitary control. In contrast with normal cats, TSH secretion is chronically suppressed during primary hyperthyroidism, and exogenous T_3 administration has little to no effect on endogenous serum T_4 concentrations. The T_3 suppression test is helpful in distinguishing mildly hyperthyroid cats from euthyroid cats; however, it requires multiple days of treatment for suppression to occur and

owner compliance is critical. Following collection of baseline serum T_3 and T_4 samples, owners are instructed to administer T_3 hormone (liothyronine; Cytomel®; King Pharmaceuticals Inc., Bristol, TN, USA) 25 μg orally three times daily for 2 days, and once on the morning of day 3, for a total of seven doses.[47] Two to four hours after the final dose is given, a second T_3 and T_4 concentration is assessed. The pre-liothyronine and post-liothyronine samples should be submitted to the laboratory at the same time to limit the influence of interassay variation. Cats with hyperthyroidism will have little to no decrease in total T_4 concentration after administration of liothyronine, while suppression of total T_4 concentration of 50% or more will occur in euthyroid cats.[47] Lack of T_4 suppression could also be the result of poor compliance with test instructions and may yield false-positive results. Compliance can be gauged by comparing T_3 concentrations before and after the test. If the liothyronine was administered correctly, the final T_3 concentration will be elevated above the initial sample. If this does not occur, owner compliance should be questioned, and the test result should be considered invalid.

TRH stimulation test

A TRH stimulation test also evaluates the integrity of the pituitary-thyroid gland feedback system via administration of TRH. TRH from the hypothalamus stimulates release of TSH from the anterior pituitary gland to increase synthesis and release of thyroid hormones from the thyroid gland. Administration of exogenous TRH to a cat with normal thyroid function will increase TSH secretion and increase serum total T_4 concentrations. To perform a TRH stimulation test, a serum T_4 sample is collected before and 4 hours after intravenous administration of 0.1 mg/kg TRH.[48] Cats with even mild hyperthyroidism should have little (<50%) or no increase in serum total T_4 concentration due to hyperthyroid-induced chronic suppression of endogenous TSH. Clinically healthy cats and cats with nonthyroid disease should have an increase in serum T_4 concentrations of >60%.[48] This test is considered as reliable as a T_3 suppression test; however, the only preparation of TRH approved by the US Food and Drug Administration is no longer available, side effects are common following administration of TRH,[48] and results can be difficult to determine, especially in cats with concurrent illness,[49] so, in general, this test is not recommended.

TSH response test

A TSH response test is typically utilized to aid in the diagnosis of hypothyroidism in dogs, but also has the potential to differentiate euthyroid cats from those with hyperthyroidism.[4] The protocol involves obtaining a baseline serum total T_4 value, followed by administration of intravenous TSH and collection of a second total T_4 sample 6–8 hours later. Hyperthyroid cats should have little or no response to exogenous administration of TSH; however, results can be difficult to interpret due to overlap in total T_4 response in euthyroid and hyperthyroid cats.[29,40,45] In addition, the bovine TSH initially utilized for this test is no longer available, and the response to administration of recombinant human TSH has not been evaluated in hyperthyroid cats. Therefore, this test is currently not recommended for the diagnosis of hyperthyroidism, and should only be utilized for diagnosis of canine hypothyroidism.[4,29,40,45]

Random TSH concentration testing

Measuring a random circulating TSH concentration to detect subclinical hyperthyroidism may be helpful. Cats with subclinical hyperthyroidism should have a low circulating TSH concentration before elevation in total T_4 occurs.[50] When evaluating hyperthyroid cats, normal cats, and cats with chronic kidney disease, it was found that all hyperthyroid cats had TSH values below the quantification value.[45] However, five of 40 nonhyperthyroid cats also had TSH levels below the quantification value, and the presence of chronic kidney disease did not appear to affect TSH concentrations.[45] Furthermore, in 104 client-owned cats, TSH concentrations were evaluated with the hypothesis that geriatric euthyroid cats with undetectable TSH concentrations would have an increased risk of developing clinical hyperthyroidism.[50] Although the cats with undetectable baseline TSH concentrations were significantly more likely to be diagnosed with hyperthyroidism within 14 months, only about half of the cats with undetectable baseline TSH concentrations became hyperthyroid within the 14-month study period.[50] Ultimately, further studies are needed to determine the utility of measuring a random circulating TSH level in cats.

Thyroid scintigraphy

If the results of thyroid hormone tests are equivocal but clinical suspicion remains high, thyroid scintigraphy should be considered to confirm hyperthyroidism. In addition to confirming hyperthyroidism, thyroid scintigraphy can also provide information that aids in treatment decisions, and is the best way to detect metastasis of malignant thyroid tumors. Multiple radionuclides have been utilized for imaging the thyroid glands. The use of radioactive iodine (^{131}I or ^{123}I) has been described; however, radioactive technetium-99m

(pertechnetate; $^{99m}TcO_4$) is the radionuclide most commonly used. $^{99m}TcO_4$ is trapped and concentrated within thyroid follicular cells because the molecular configuration of $^{99m}TcO_4$ mimics the size and charge of iodide.[4,51] $^{99m}TcO_4$ is the radionuclide of choice for routine thyroid imaging due to its low cost, short half-life, rapid uptake by the thyroid, low-energy γ-particle emission, and lack of β-emission.[4,51] After intravenous injection of $^{99m}TcO_4$, concentration of the radionuclide within the thyroid tissue occurs over 20–120 minutes and all functioning thyroid tissue can be detected using a gamma camera.[2,4,51–53] In normal cats, pertechnetate concentrates in salivary and thyroid tissue to a similar degree, and to a lesser degree in epithelial tissues such as the gastric mucosa.[51] The normal thyroid glands are elongated ovals of similar size and location bilaterally. Thyroid activity is assessed by comparing the ratio of $^{99m}TcO_4$ uptake by the thyroid gland with uptake by the zygomatic molar salivary gland using a region of interest drawn around the salivary tissue and thyroid tissue (Figure 1). The thyroid to salivary gland uptake ratio is approximately 1:1 in normal cats and more than 1:1 in hyperthyroidism.[51,52] The increase in thyroid to salivary ratio is directly proportional to thyroid gland function.[52]

As previously discussed, most hyperthyroid cats have bilateral disease, even if not appreciated by cervical palpation. Thyroid scintigraphy allows the extent of abnormal thyroid tissue to be determined. Scintigraphy in cats with true unilateral thyroid disease will reveal only one active thyroid gland because chronic TSH suppression leads to atrophy of the contralateral gland. In contrast, both thyroid glands are detected in cats with bilateral disease, despite the lack of circulating TSH. Bilateral hyperthyroidism typically results in asymmetric thyroid enlargement. The literature has reported that 3%–20% of hyperthyroid cats have abnormal functional thyroid tissue located in the cranial mediastinum, which can only be detected with scintigraphy.[4,54] Although histopathology remains the gold standard for the diagnosis of thyroid carcinoma, thyroid scintigraphy can aid in the presumptive diagnosis via detection of masses that cannot be palpated. Although one report found no reliable features on scintigraphy to distinguish thyroid carcinoma from adenoma,[55] others have described associations between malignancy and certain radionuclide uptake patterns. The patterns that have been associated with malignancy include uptake in the cranial mediastinum, detection of multiple and extensive regions of uptake, distorted, irregular uptake with activity extending beyond the thyroid gland margins, and detection of linear multifocal uptake patterns.[3,56,57]

Thyroid ultrasound

Ultrasonography can be utilized to evaluate the architecture of the thyroid glands; however, it is not useful for the diagnosis of hyperthyroidism. The normal feline thyroid gland is thin, fusiform-shaped, and approximately 15–25 mm in length, with uniform echogenicity and surrounded by a thin, hyperechoic capsule.[4] Thyroid ultrasound examination of 15 hyperthyroid cats revealed thyroid glands that were larger with rounded margins, mixed echotexture, and increased vascularity compared with the appearance of the same glands 6 months after successful ^{131}I therapy.[58] Sonographically determined volumes of single adenomatous glands from hyperthyroid cats were in the range of 552–572 mm^3 compared with thyroid volumes in the range of 40–140 mm^3 in cats with normal thyroid function.[58,59]

Treatment options

The major modalities currently available for the treatment of cats with hyperthyroidism include noncurative medical management with methimazole (Tapazole®; King Pharmaceuticals Inc.) and dietary management with Hill's y/d® prescription diet (Hill's Pet Nutrition, Topeka, KS, USA) or curative therapy with surgery (thyroidectomy) and/or radioactive therapy (^{131}I). Each treatment modality
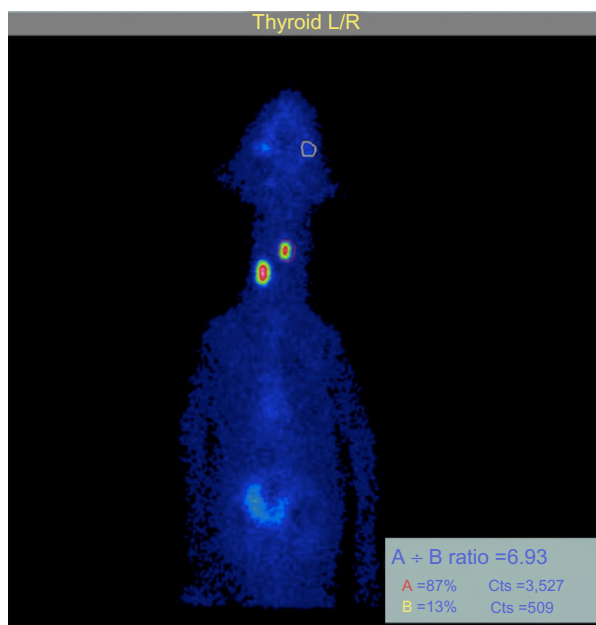

Figure 1 Cat with bilateral hyperthyroidism as seen by uptake of pertechnetate in both hyperplastic thyroid glands.
Notes: Note the region of interest around the left zygomatic molar salivary gland, as well as mild pertechnetate uptake in the gastric mucosa. The left thyroid to left zygomatic molar salivary gland ratio is 6.93.
Abbreviations: A, thyroid gland; B, zygomatic salivary gland; Cts, counts; L, left; R, right.

has advantages and disadvantages, and treatment decisions should be based on the needs of each individual cat and its owner.

Methimazole

Medical management using oral methimazole is a commonly used noncurative treatment modality in the USA. Oral methimazole therapy provides an opportunity to adjust the dosage of antithyroid medication over time as needed; however, noncurative treatment necessitates daily lifelong administration of medication to control hyperthyroidism. Methimazole is a thioureylene compound that blocks the synthesis of thyroid hormones by inhibiting thyroid peroxidase activity, leading to reduced organification of iodide, as well as inhibition of the coupling of iodothyronines to form T_3 and T_4.[60] Methimazole does not inhibit the release of preformed, stored thyroid hormone, which delays the normalization of T_4 concentrations by 2–4 weeks after initiating therapy.[39] Methimazole has a serum half-life of 2.3 hours in hyperthyroid cats and 4.7 hours in normal cats.[60,61] Carbimazole, another antithyroid medication, is metabolized to methimazole after oral administration, making it as effective as methimazole. Carbimazole is widely used in Europe and Asia for the treatment of feline hyperthyroidism but is not licensed for this indication in the USA.[29]

Evaluation of 262 hyperthyroid cats treated with methimazole as the sole therapy revealed a decrease in T_4 concentration after 2–3 weeks of therapy.[39] Side effects associated with oral methimazole were reported in approximately 18% of treated cats, and included vomiting, anorexia, and depression, as well as self-induced excoriations of the face or neck, blood dyscrasias, and hepatopathy.[39] These effects are typically observed within 2–4 weeks of initiation of methimazole therapy. If less severe side effects such as vomiting are observed, a decrease in methimazole dose can be attempted; however, if the more serious blood dyscrasias or hepatopathy occur, methimazole should be discontinued immediately, and supportive care should be instituted as necessary.

The recommended starting dose is 2.5 mg methimazole orally twice daily.[4,62] Although once-daily dosing has been advocated, twice-daily dosing has been found to be more effective.[63] After 2–3 weeks on the starting dose, the serum total T_4 should be determined; the target total T_4 concentration is in the lower half of the reference interval.[62,63] A recent study determined that the timing of blood collection after administration of methimazole is not crucial and does not affect the ability to assess the therapeutic response.[64] Continued monitoring of total T_4 concentrations should be done every 2–3 weeks after a dosage change, 3 months after initial stabilization of total T_4, and every 6 months

thereafter.[62] If the serum total T_4 concentration at recheck is within or just above the reference interval, the dose should be maintained. If the serum total T_4 value is below the reference interval, a dose reduction of 2.5 mg per day is indicated.[62] If serum total T_4 remains significantly elevated despite therapy, compliance should first be assessed, and if judged adequate, the methimazole dose should be increased by 2.5 mg per day.[4,62] Although the effects of methimazole on total T_4 values are typically observed within the first week of initiation of therapy, resolution of clinical signs may not be observed for up to 6 weeks after euthyroidism is restored.[4]

Hyperthyroid cats with concurrent chronic kidney disease can present a treatment dilemma. Multiple studies have confirmed that treatment of hyperthyroidism with methimazole (as well as ^{131}I and thyroidectomy) decreases the glomerular filtration rate.[65–67] Although the decrease in glomerular filtration rate is a result of return to a euthyroid state rather than a consequence of the particular antithyroid therapy used, the decreased renal excretion can either unmask previously undiagnosed chronic kidney disease or exacerbate known chronic kidney disease. In non-azotemic cats with unrecognized early chronic kidney disease, it remains difficult to predict the magnitude of the decrease in glomerular filtration rate or the development of azotemia following successful treatment of hyperthyroidism. For this reason, it is historically recommended that treatment of cats with previously diagnosed renal disease start at a lower dose of methimazole, such as 1.25 mg twice daily or 2.5 mg once daily. In addition, a trial with oral methimazole is often recommended prior to pursuit of either thyroidectomy or ^{131}I to assess possible adverse renal function effects after restoration of euthyroidism.

During oral methimazole therapy, most cats exhibit only mild changes in renal function (<30% increase in serum creatinine), which stabilizes within approximately 1 month after successful treatment of hyperthyroidism.[32,67] In addition, although it is not uncommon for cats to experience azotemia after successful treatment of hyperthyroidism, it has been shown that those cats that develop azotemia post-methimazole or I^{131} therapy do not have a decreased overall survival time compared with cats that remain non-azotemic when treated for hyperthyroidism.[68] There is increasing evidence that maintenance of a hyperthyroid state is detrimental to long-term renal function. For example, when evaluating the N-acetyl-β-D-glucosaminidase index (NAG_i), a specific marker of active proximal tubular damage, in 24 non-azotemic hyperthyroid cats treated with methimazole, the high NAG_i levels in hyperthyroid cats decreased following therapy, indicating that the renal changes associated with hyperthyroidism can be reversed.[69] Therefore, despite the risk of reduced renal

function, maintaining total T_4 values in the lower half of the reference interval is indicated for affected cats unless there is a profound increase in azotemia that adversely affects the cat's quality of life.

Although post-therapy azotemia, in the absence of pre-therapy azotemia, has not been associated with decreased survival times, cats with hyperthyroidism and evidence of pre-existing chronic kidney disease treated with oral methimazole or ^{131}I had significantly shorter survival times than hyperthyroid cats without evidence of renal disease.[70] Overall, the median survival time of cats treated with methimazole alone has been reported as approximately 2 years, while those treated with methimazole followed by ^{131}I had a median survival time of 5.3 years.[70] Another study of 300 hyperthyroid cats treated with oral methimazole or carbimazole alone or in combination with thyroidectomy found the overall median survival time to be 417 days.[20] Of these 300 cats, the hyperthyroid cats with pre-therapy azotemia had a significantly shorter median survival time (178 days) than non-azotemic cats (612 days).[20]

In addition to oral methimazole, compounded topical preparations of methimazole are available that are absorbed transdermally. Initial studies reported the bioavailability of transdermal methimazole to be poor after application of a single dose to the pinnae of healthy cats.[71] However, long-term use of topical methimazole decreased total T_4 concentrations and resulted in restored euthyroidism.[72] Although the overall efficacy of transdermal methimazole was less than that of oral methimazole, and oral methimazole was significantly more effective than the transdermal formulation at 2 weeks post-therapy, the initial difference in T_4 concentrations was no longer significant by 4 weeks post-therapy.[73] These data suggest that chronic use of transdermal methimazole can be effective in lowering T_4 concentrations.[73] The recommended initial dose of the transdermal formulation is 5–10 mg per cat, and once-daily application appears to be as effective in controlling total T_4 as twice-daily application.[74,75] Gastrointestinal side effects were found to occur less frequently with the transdermal formulation than with the oral formulation.[73] Additional adverse effects associated with the transdermal formulation include mild crusting and erythema at the site of application. Overall, transdermal methimazole may be a viable option for some patients, but it must be remembered when using compounded medications that different compounded products can vary in efficacy and safety.

Hill's y/d® prescription diet

Dietary iodine restriction is a newly developed therapy for feline hyperthyroidism. The only available commercial diet for the management of feline hyperthyroidism is Hill's y/d prescription diet. The diet is markedly restricted in iodine content, which requires strict dietary compliance for successful management of hyperthyroidism, and concurrent use of this diet and methimazole is not recommended.[76] Iodine is the major mineral component of thyroid hormones and its only known biologic function is the production of T_3 and T_4 hormones.[36] Iodine content in commercial cat foods varies widely, ranging from undetectable to greater than 35 ppm. The absolute dietary iodine requirements for cats are unknown. Precise requirements are difficult to determine since the thyroid gland is able to adapt its function to wide variations in iodine intake, and other dietary ingredients such as perchlorate can interfere with thyroid usage of iodine and iodine measurements by analytical methods.[36]

The effects of dietary iodine restriction on the thyroid gland were evaluated by feeding nine cats with naturally occurring hyperthyroidism diets containing either 0.47 ppm, 0.28 ppm, or 0.17 ppm iodine on a dry matter basis.[77] When fed either the 0.47 ppm iodine or 0.28 ppm iodine diet, eight of the nine cats became euthyroid, while all nine cats became euthyroid when fed the 0.17 ppm iodine diet.[77] There were no adverse effects noted in any of the cats while feeding any of the iodine-restricted diets.[77] The study concluded that iodine restriction is safe and effective for returning hyperthyroid cats to a euthyroid state.[77] A subsequent study showed that hyperthyroid cats had significantly reduced serum total T_4 concentrations at 0, 3, 6, and 12 weeks when dietary iodine was reduced from 1.9 ppm to 0.32 ppm.[78] The results of feeding studies show that diets with ≤0.32 ppm iodine lower serum total T_4 in cats with naturally occurring hyperthyroidism.[77–79]

In a study of client-owned hyperthyroid cats, feeding iodine-restricted food (0.32 ppm on a dry matter basis) decreased total T_4 concentration and improved clinical signs after consuming the diet for 4 weeks.[80] No adverse effects associated with feeding the iodine-restricted diet were observed. Although dietary iodine restriction appears to be a valid option in the management of hyperthyroidism in a subset of hyperthyroid cats in which strict dietary compliance can be achieved, there is concern that many cats do not achieve total T_4 values in the lower half of the reference interval, indicating optimal control of hyperthyroidism may be difficult via modification of diet alone.

Thyroidectomy

Thyroidectomy is curative for feline hyperthyroidism, but the popularity of surgical treatment has declined over the past decade, in part due to the risk of significant postoperative complications and because of the development and availability

of nonsurgical treatment options. Since over 70% of hyperthyroid cats have bilateral thyroid disease,[2] curative surgery requires bilateral thyroidectomy for most cats.[81] Multiple surgical procedures have been described,[81–84] but complete discussion of surgical approaches is beyond the scope of this review. Morbidity associated with surgical approaches results from disruption of important structures in proximity to the thyroid glands, including the parathyroid glands, the carotid arteries, jugular veins, and recurrent laryngeal nerves. The most serious postoperative complication is severe hypocalcemia caused by iatrogenic damage or removal of the parathyroid gland(s) during surgery.[81–83] Horner's syndrome and laryngeal dysfunction (voice change) or laryngeal paralysis are other possible surgical complications.[81–83] Along with surgical complications specific to the thyroidectomy, geriatric hyperthyroid cats are often in poor body condition and may have other concurrent disease(s), making them less desirable anesthetic candidates. In addition to surgical complications, treatment failures can also occur either due to persistent hyperthyroidism or permanent hypothyroidism. Persistent hyperthyroidism can result from incomplete thyroidectomy, or presence of ectopic thyroid tissue, while permanent hypothyroidism can result from removal of all functional thyroid tissue via bilateral thyroidectomy.[81–83]

Of 101 cats that underwent either unilateral or bilateral thyroidectomy, two died within 72 hours of surgery. Follow-up 59 months after thyroidectomy revealed 57 cats were still alive with a median survival time of 1.9 years, and 44 cats that were no longer alive had had a median survival time of 1.1 years.[85] Reported causes of death included renal failure, other malignant tumors, megacolon, aortic thrombosis, respiratory problems, seizures, urinary tract problems, viral infections, and liver disease. Ultimately, if thyroidectomy is chosen as the primary treatment for hyperthyroidism, euthyroidism should be achieved prior to surgery via medical or dietary management. Euthyroidism at the time of surgery may diminish the risk of cardiac complications associated with anesthesia and permits assessment of renal function prior to thyroidectomy.

Radioiodine therapy

Radioactive iodine (^{131}I) is a curative treatment for feline hyperthyroidism and is the treatment of choice for most cats due to its high cure rate and minimal side effects. Because iodine transporters on thyroid cells do not differentiate radioactive iodine from naturally occurring iodine, the radioactive isotope is able to concentrate within the thyroid gland. ^{131}I emits β-particles and γ-rays, which destroy any surrounding functional thyroid tissue.[4] β-particles are responsible for the majority of the clinical effect by causing pyknosis and necrosis of thyroid follicular cells as well as vascular and stromal fibrosis of the gland.[4] The emitted radiation travels on average only 400 μm within thyroid tissue and spares surrounding tissues such as the parathyroid glands.[4] In addition, atrophied thyroid tissue is unaffected by ^{131}I due to its inability to uptake iodine, making ^{131}I the only treatment modality to specifically target hyperfunctioning thyroid tissue.[86]

^{131}I is typically administered by subcutaneous injection, although intravenous and oral administration is also acceptable.[40] Several methods for calculating an ^{131}I dose have been described.[3,4,87,88] Ultimately, treatment protocols that use variable ^{131}I doses (tailored to individual cats) have no advantage over protocols that employ a fixed ^{131}I dose, so most treatment centers report use of a fixed-dose protocol that administers 3–6 mCi per cat.[40,54,86,87] A study that evaluated 524 hyperthyroid cats treated with radioiodine used a single dose of 2–6 mCi ^{131}I.[40] The administered dose was determined using a combination of severity of clinical signs, magnitude of serum T_4 elevation, and size of the thyroid gland(s) measured by digital palpation.[40] The investigators reported that there was complete resolution of clinical signs of hyperthyroidism and return of serum total T_4 concentration to within the reference interval in 94.2% of cases within 6–12 months of radioiodine therapy; only eight cats remained hyperthyroid and eleven developed clinical hypothyroidism 12 months after ^{131}I treatment. Based on these results, it is recommended that cats that remain hyperthyroid after an initial ^{131}I treatment should not undergo a second treatment until persistent hyperthyroidism has been documented at 6 months post-therapy.[40]

^{131}I doses of 10–30 mCi carry the best chance of completely destroying malignant thyroid tissue, making it the treatment of choice in cats with confirmed thyroid carcinoma, regardless of tumor location, including pulmonary metastases.[3,89] Larger doses of ^{131}I are needed for carcinomas because malignant thyroid cells do not concentrate or retain ^{131}I as effectively as adenomatous cells.[3,55,89] The use of high-dose radioiodine in cats after thyroidectomy for carcinoma has been associated with a high rate of post-treatment hypothyroidism requiring thyroxine supplementation.[89] However, another study that evaluated a single high dose of ^{131}I as the sole therapy, found that six of seven cats with confirmed thyroid carcinoma had complete clinical resolution of hyperthyroidism and none of the cats had clinically significant hypothyroidism requiring supplementation post-^{131}I treatment.[55]

Potential disadvantages of ^{131}I therapy include persistent hyperthyroidism requiring a second ^{131}I treatment or use of antithyroid medication, as well as post-^{131}I treatment hypothyroidism.[40,86] Of 524 cats treated with a mean radioiodine dose of 3.4 mCi, the percentage of cats with relapse of hyperthyroidism was only 2.5% and the prevalence of clinical hypothyroidism requiring thyroid supplementation was only 2.1%.[40] Additional disadvantages of radioiodine therapy include the need for patients to be housed separately for 7–10 days after treatment or until radioactivity falls to safe levels as determined by state regulations. After discharge from the hospital, many cats will continue to emit low doses of radiation for approximately 2 weeks, which necessitates additional precautions be implemented to avoid unnecessary exposure of pet owners. In addition to specific in-hospital housing requirements, staff with radiation safety training are needed to care for the cats in the post-treatment period. Due to these factors, there is a relatively high upfront (but one time) cost for ^{131}I therapy.

In general, ^{131}I is a highly efficacious treatment modality, with 95% of cats becoming euthyroid within 3 months of receiving a single treatment.[4] The median survival times associated with ^{131}I therapy have been found to be comparable with or longer than those reported for cats that undergo surgical thyroidectomy.[85] The median survival time of the abovementioned 524 cats that received ^{131}I was approximately 2 years.[40] Other reported median survival times for cats that received ^{131}I for treatment of hyperthyroidism are 25 months[90] and 4 years.[70] Overall, due to the high efficacy rate for controlling feline hyperthyroidism, as well as the low incidence of adverse effects, ^{131}I remains the curative treatment of choice for feline hyperthyroidism.

Treatment-associated hypothyroidism

Upon instituting therapy for hyperthyroidism, in addition to monitoring total T_4 concentrations to ensure euthyroidism, one must also consider the potential for iatrogenic hypothyroidism. Not all cats with decreased total T_4 values exhibit clinical signs of hypothyroidism. Hypothyroidism has been associated with decreased glomerular filtration rate, and thus could have significant consequences in cats with pre-existing renal disease. Cats that developed iatrogenic hypothyroidism had a greater incidence of azotemia than cats that were euthyroid following treatment for hyperthyroidism.[32] In addition, cats with iatrogenic hypothyroidism were more likely to develop azotemia within 6 months after treatment of hyperthyroidism, and hypothyroid cats with azotemia have decreased survival times compared with hypothyroid

non-azotemic cats.[32,91] Finally, it has been demonstrated that restoration of euthyroidism via dose adjustments of antithyroid medication in cats with iatrogenic hypothyroidism improves renal function.[92]

Conclusion

Hyperthyroidism is the most commonly diagnosed endocrinopathy in older cats, and its recognition and diagnosis are important for small animal practitioners. The pros and cons of the available treatment options as well as long-term monitoring requirements should be discussed in detail with cat owners to ensure the most appropriate treatment plan is initiated for each individual cat. The costs associated with each treatment option vary based on the facility, and the relatively larger upfront cost of thyroidectomy and ^{131}I must be compared with the monthly costs associated with the noncurative treatment options. Due to the lack of a randomized trial evaluating all the different treatment options, it is difficult to state the superiority of one treatment modality over the other, emphasizing the need to tailor therapy to each individual cat and owner needs.

Disclosure

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