Feline Hyperthyroid Update: Some Things Old, But Everything New

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Since hyperthyroidism (thyrotoxicosis) was first described in cats in 1979, it has emerged as the most common endocrine disorder of this species, as well as a disease frequently diagnosed in small animal practice. It is unclear if this represents a true increase in the incidence of the disease, an increased awareness of the condition by practitioners and clients, a growing pet cat population coupled with increased longevity, or a combination of these factors.

ETIOPATHOLOGIC FINDINGS OF HYPERTHYROIDISM IN CATS

Benign adenomatous hyperplasia (adenoma) of one, or more commonly, both thyroid lobes is the most common pathological abnormality associated with hyperthyroidism in cats. Microscopically, the normal thyroid follicular architecture is replaced by one or more readily discernible foci of hyperplastic tissue forming nodules ranging from less than 1-mm to over 2-cm in diameter (1).

By contrast, thyroid carcinoma is a rare cause of hyperthyroidism in cats accounting for less than 2% of cases (1,2). Recently, investigators have presented evidence showing that some hyperthyroid cats may have areas of adenoma adjacent to areas of carcinoma within the same thyroid lobe upon biopsy (3,4). This could suggest that, at least in some cats with long-standing hyperthyroidism, there may be transformation of thyroid adenomatous hyperplasia or adenoma to thyroid carcinoma. If that is the case, the difference in behavior and response to treatment between cats with thyroid adenoma vs. thyroid carcinoma may be related primarily to the greater tumor volume of the cats with carcinoma rather than a marked difference in tumor behavior between the two groups. In support of this, most cats with thyroid carcinoma have a larger tumor burden with local extension of the tumor rather than widespread metastasis to the lungs or other organs.

Although great strides have been made in the diagnosis and treatment of cats with hyperthyroidism, the underlying cause(s) of this disorder remains unknown. None of the studies to date have isolated a single dominant factor that could be incriminated in the development of hyperthyroidism in cats (5). Rather, most of the studies provide further evidence of the widely held view that hyperthyroidism is a multifactorial disease in this species.

At this time, the most likely candidates include one or more of the goitrogenic chemicals (sometimes referred to as “Thyroid Disruptors”) that have been shown to be present in cat food or the environment (or both). For instance, liners of the easy open ‘pop-top’ cans have been shown to contain the plasticizer bisphenol-A-diglycidyl ester (BADGE), a compound suspected to leach into the canned foods consumed by cats (6). Investigators have also implicated flame retardants such as polybrominated diphenyl ethers (PBDEs) that could act as environmental goitrogens in cats, since cats had serum levels of these compounds that were 10- to 400-fold higher than the average human (7). Recently, undersupplemented pet food and iodine deficiency has been suggested to also play a role (8). Finally, mutations of the thyroid

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stimulating hormone receptor gene or mutations of its associated G proteins also seem to play an important role in the pathogenesis of this disease (5).

**UPDATE ON DIAGNOSTIC TESTING FOR HYPERTHYROIDISM**

In most cats, the diagnosis can easily be confirmed on the basis of signalment (older than 10 years), clinical signs (weight loss despite good appetite), characteristic physical examination finding (palpation of thyroid nodule), exclusion of nonthyroidal diseases, and the finding of a high serum T4 value (1,9). In the majority of hyperthyroid cats with reference range total T4 concentration, repeat total T4 analysis or simultaneous measurement of free T4 allows for confirmation of the diagnosis. Further diagnostic tests are rarely required.

If hyperthyroidism is suspected based upon history, clinical signs (weight loss despite a good appetite), and examination findings (tachycardia, palpable thyroid nodule) but the serum total and free T4 remains only borderline high, hyperthyroidism is still possible. In this case, the most definitive test to do is thyroid scintigraphy (thyroid scanning).

**Scintigraphy**

Thyroid scintigraphy is a nuclear medicine procedure that produces a visual display of functional thyroid tissue based on the selective uptake of various radionuclides by thyroid tissue (9). Thyroid scintigraphy is able to identify thyroid disease and define the degree of that thyroid disease relatively unaffected by the presence of concurrent nonthyroidal illness. Because thyroid scintigraphy directly visualizes functional thyroid tissue, thyroid imaging can diagnose hyperthyroidism before laboratory tests are abnormal. Thyroid scanning can also prevent misdiagnosis of hyperthyroidism in cats with falsely high serum T4 values (10,11).

**TREATMENT OF SEVERE, UNRESPONSIVE, OR RECURRENT HYPERTHYROIDISM**

Most hyperthyroid cats, at least in the early stages of their disease, can be readily controlled with antithyroid drugs. Similarly, most cats with mild to moderate hyperthyroidism are cured quite easily with standard “low” doses of radiiodine (12,13) or by use of surgical thyroidectomy (1). Occasionally, the practicing veterinarian will see hyperthyroid cats that become unresponsive to antithyroid drug treatment, generally after months of satisfactory control. Other cats treated with either thyroidectomy or radiiodine remain persistently hyperthyroid or experience relapse shortly after treatment. Such problematic hyperthyroid cats can be frustrating to manage, especially as their disease becomes more severe and they develop complications of advanced or poorly controlled hyperthyroidism.

Poor response to long-term treatment with methimazole is a relatively common problem seen in hyperthyroid cats. Because these antithyroid drugs do not slow or stop thyroid tumor growth, the thyroid goiter in these cats tends to grow progressively larger with time. After 1-3 years or more, many of these cats will develop very large, palpable goiters and will become difficult to regulate, even with high daily doses of oral or transdermal methimazole. Eventually, it may be difficult to impossible to raise the antithyroid drug dose to one high enough to keep maintain circulating thyroid values even close to the normal reference range.
As the disease progresses over time, the thyroid adenoma adenomatous hyperplasia in some hyperthyroid cats will also transform into malignant thyroid carcinoma (3,4). Again, methimazole or other antithyroid drug therapy does nothing to the thyroid tumor pathology and cannot stop this from happening.

All practicing veterinarians should always explain to all owners of cats with hyperthyroidism that the disease is caused by a thyroid tumor, and that this tumor will gradually grow progressively larger with time. If methimazole is used as initially treatment, they should be told that the antithyroid drug may eventually stop working and that other treatments may be needed. However, both surgery and radioiodine can be more difficult to achieve a cure in cats with extremely large goiters, even if the thyroid tumors are benign, so early definitive therapy is always best. In cats that are young to middle-aged, it is not logical (at least to me) to treat with methimazole on a long-term basis unless you do not believe that the cat will live for more than a year or two or the owner refuses definitive therapy.

As someone who does thyroid imaging and radioiodine treatment, I see a couple of cats each month that have been treated for years with antithyroid drugs and now have very large to huge thyroid tumors. In about 10% of these cats with severe, long-standing hyperthyroidism, the diagnosis is thyroid carcinoma with extension of tumor or metastasis into the chest. It’s quite likely that transformation of the tumor from adenoma to carcinoma has occurred in these cats.

Cats with huge benign or malignant tumors require much larger doses of radioiodine to ablate (10 to 30 mCi) the thyroid tumor(s) than do the typical recently diagnosed cats with mild to moderately hyperthyroidism (2 to 6 mCi). These cats with severe, advanced thyroid disease can generally be cured with high-dose radioiodine treatment, but it is much more difficult to cure them with a single dose.

Thyroid carcinoma must always be suspected if the palpable goiter is extremely large, serum total T4 is particularly high, or if hyperthyroidism persists despite high doses of methimazole or carbimazole. However, each of these criteria may also apply to benign hyperthyroidism. Lack of response to increasing doses of antithyroid drugs, persistent hyperthyroidism, or rapid recurrence following routine bilateral thyroidectomy or radioiodine therapy should all should alert the clinician of the possibility of malignancy. While thyroid carcinoma in cats appears to be rare, many cases appear to go undiagnosed, at least in the earlier stages of disease. Diagnosing thyroid carcinoma is very important because standard treatment strategies for hyperthyroidism almost always fail to manage this malignant condition adequately.

EFFECT OF HYPERTHYROID TREATMENTS ON RENAL FUNCTION
Chronic kidney disease (CKD) and hyperthyroidism often occur together because they are both common disorders of older cats. Hyperthyroidism tends to artificially increase glomerular filtration rate (GFR), an effect that can mask underlying renal insufficiency. Thus, if blood tests taken to assess kidney function in a hyperthyroid cat are normal or show only mild changes, moderate to severe renal failure may still be present. All treatments for hyperthyroidism, by restoring high serum T4 concentrations to normal, tend to decrease GFR to normal or low levels and may “worsen” kidney function tests (14). It is important to remember that treatment of
hyperthyroidism itself does not cause the renal disease; it was already present before treatment, but it may have been masked by the cat’s abnormally high GFR.

The prevalence of CKD in general feline population has been reported to be 7.7% of cats >10 years of age and 15.3% of cats >15 years of age (16). In contrast, the prevalence of CKD in hyperthyroid cats has been estimated to be as high as 30-40% (15). This much higher-than-expected prevalence of chronic kidney disease in hyperthyroid cats suggests that untreated thyrotoxic state is initiating or worsening the CKD in these cats. If that is true, one may want to always try to correct the cat’s hyperthyroidism, even in cats with known CKD.

In cats with hyperthyroidism, local activation of the renin-angiotensin-system at the level of the kidney may lead to glomerular capillary hypertension, proteinuria, and hyperfiltration of nephrons, all of which may contribute to the development or progression of renal disease. A recent study by van Hoek and colleagues (16) showed that urine protein excretion decreased significantly in cats after radioiodine treatment. In addition, high levels of retinol binding protein, a marker for renal tubular damage, also decreased significantly after radioiodine treatment, also suggesting a reversible type of renal dysfunction (17,18).

Leaving a cat’s hyperthyroid state untreated (or poorly regulated with methimazole) may be detrimental to kidney function in the long term. Treating and successfully curing hyperthyroidism, on the other hand, may help preserve the remaining kidney function by decreasing glomerular hypertension and the hyperfiltration of nephrons.

Predicting which untreated hyperthyroid cats have clinically significant underlying CKD is difficult (21). In the absence of methods for accurately measuring GFR in veterinary practice, serum urea and creatinine concentrations, urine specific gravity, and UPC should be carefully evaluated in individual cases. If any parameter is abnormal, then renal failure may become apparent upon resolution of the hyperthyroid state.

Because of these difficulties, trial therapy using methimazole has been recommended as a test of renal function. If deterioration in renal function does not occur after medical normalization of the T4 values, then a more definitive therapeutic option for hyperthyroidism may be selected. Except for advanced CKD, the necessity of this approach is questionable, given that treatment for the hyperthyroidism would still recommended in most cats. In support of that reasoning, the survival of cats that develop azotemia is no different to those that remain non-azotemic after treatment of hyperthyroidism (19).

In most hyperthyroid cats that manifest overt renal disease after antithyroid drug treatment, permanent treatments with surgery or radioiodine can be given once the concurrent renal disease is stabilized with proper treatment (e.g., subcutaneous fluids, phosphate binders). It is important to realize that the decline in GFR following initial treatment of hyperthyroidism is not progressive with long-term euthyroidism; once serum T4 concentrations have fallen into the normal range, the GFR tends to stabilize at that new rate.

In most cats that develop post-treatment azotemia, the CKD is not that severe or life threatening. It is also unusual to see a jump of more than one IRIS stage after treatment (20). In other words, hyperthyroid cats with IRIS Stage I-II CKD may develop overt azotemia after treatment, but one would not expect those cats’ CKD to advance to more than IRIS Stage II-III after treatment.

In addition, the decline in GFR after successful treatment of a cat’s hyperthyroidism is not very progressive. Rather, the fall in GFR is detectable within 1 month but then remains
stable at this level for months thereafter. The rise in serum urea nitrogen and creatinine values in cats with CKD follow the decrease in GFR, so that azotemia, when it does occur, would be expect to develop within 1 month of treatment but remain relatively stable over many months.

**EFFECT OF IATROGENIC HYPOTHYROIDISM ON RENAL FUNCTION**

Whatever treatment option for hyperthyroidism is considered, it is extremely important to avoid hypothyroidism as it may have its own detrimental effects on GFR. Hypothyroidism in both humans and dogs has been showed to reduce GFR (21), and it is likely that similar changes occur in cats that develop iatrogenic hypothyroidism.

In recent studies by Williams et al (22-24), cats with iatrogenic hypothyroidism were more likely to develop azotemia in the 6 months after treatment than cats that remained euthyroid. Hypothyroid cats with azotemia also had shorter survival times than nonazotemic cats, whereas no difference in survival between euthyroid cats with or without azotemia could be detected. This suggests that the development iatrogenic hypothyroidism contributes to the development of azotemia, at least in cats with mild underlying CKD (IRIS Stage I or II). More importantly, the hypothyroidism may shorten survival after treatment of hyperthyroidism.

If a cat with post-treatment azotemia develops a low T4 concentration, a serum TSH level should be measured to help exclude hypothyroidism. If iatrogenic hypothyroidism is diagnosed, treatment with L-thyroxine (0.1 mg once to twice daily) is indicated. The dosage should be adjusted based on post-pill serum T4 and cTSH determinations. Most cats treated will show improvement in their azotemia as the hypothyroidism resolves and euthyroidism is restored (25).

**References**


