Hyperthyroidism is the most common endocrinopathy affecting middle-aged to older cats with a 10% prevalence in cats over 10 years of age in the US. The diagnosis of hyperthyroidism is relatively straightforward in most cases but can be challenging in cats with mild hyperthyroidism or in cats with concurrent nonthyroidal illness.

**Diagnosis of Hyperthyroidism**

Hyperthyroidism occurs due to excess thyroid hormone (thyroxine, T4 and triiodothyronine, T3) production from benign thyroid adenomas and, rarely, from thyroid carcinomas. Clinical signs typically include weight loss, polyphagia, PU/PD, hyperactivity, vomiting, diarrhea, unkempt hair coat, and increased vocalization. Abnormalities on physical examination may include tachycardia, heart murmur, arrhythmias, palpably enlarged thyroid glands, and muscle loss. Differential diagnoses to consider for cats presenting with signs consistent with hyperthyroidism include diabetes mellitus, malabsorptive GI disease (inflammatory bowel disease or lymphoma), and chronic kidney disease (CKD) necessitating further evaluation (e.g. CBC, Chemistry, and Urinalysis) prior to or in addition to thyroid hormone testing to rule out nonthyroidal illnesses. The majority of hyperthyroid cats will have a palpable thyroid nodule on physical examination; however, a palpable thyroid nodule is also possible in biochemically euthyroid cats. A finding of an enlarged thyroid gland supports but does not confirm a diagnosis of hyperthyroidism requiring further evaluation of thyroid function.

Definitive diagnosis of hyperthyroidism includes documenting persistently elevated thyroid hormones in a cat with at least one or more clinical signs of hyperthyroidism. The diagnostic approach to cats with suspected hyperthyroidism will vary depending on the presence or absence of clinical signs and physical examination findings consistent with hyperthyroidism and the presence of concurrent nonthyroidal illness.

**Total T4**

Total thyroxine (TT4) is screening test of choice for feline hyperthyroidism. TT4 will be elevated in 90% of cats with hyperthyroidism and within the mid to high reference range in 10% of hyperthyroid cats. Cats with early or mild hyperthyroidism can have TT4 that fluctuates in
and out of the reference range. About 80% of hyperthyroid cats with TT4 within reference range have early or mild hyperthyroidism and the other 20% having nonthyroidal illness. The degree of TT4 suppression from nonthyroidal illness typically correlates with the severity of illness. As such, cats with hyperthyroidism may have TT4 suppressed into mid-to-high end of the reference range due to concurrent nonthyroidal illness, and very rarely, in the low end of the reference range with severe nonthyroidal illness. If the history, clinical signs, and physical examination findings are consistent with hyperthyroidism, a normal TT4 does not exclude hyperthyroidism. Further evaluation includes repeating TT4 in 4 weeks or performing additional tests of thyroid function to confirm or exclude hyperthyroidism. Conversely, finding an elevated T4 in a cat does not always confirm hyperthyroidism as false positives are possible, although, rare. If a finding of an elevated TT4 occurs in a cat that lacks clinical signs of hyperthyroidism and absence of a palpable thyroid nodule then repeating TT4 measurement is recommended.

**Free T4**

Although Free T4 (fT4) is more sensitive than TT4 for the diagnosis of hyperthyroidism, it poorly specific. Nonthyroidal illness can result in an elevation of fT4. As such, fT4 should not be used as a first line screening test or a sole diagnostic test for feline hyperthyroidism and should always be interpreted concurrently with TT4 +/- canine TSH in a cat with clinical history suspicious for hyperthyroidism. An elevated fT4 with a high normal TT4 in a cat with clinical signs and examination findings consistent with hyperthyroidism supports a diagnosis of hyperthyroidism (either mild hyperthyroidism or concurrent NTI). Importantly, 30% of these cats with a TT4 within upper half of reference range with a high free T4 may be revealed as euthyroid further highlighting the important of interpreting these test results in light of clinical history, signs, and examination findings. A finding of a high fT4 with a TT4 with low or low normal range likely reflects NTI in a euthyroid cat.

**TSH**

Currently, a feline specific TSH assay is not available. Canine TSH assay is used for evaluation of TSH in cats; however, the cTSH assay cannot distinguish undetectable and low-normal TSH concentrations. About 98% of cats with hyperthyroidism had undetectable TSH, and up to 30% of euthyroid cats also had undetectable cTSH demonstrating the limitations of using cTSH alone for diagnosis of hyperthyroidism. Finding an undetectable cTSH in a euthyroid cat has been associated with an increased risk of developing hyperthyroidism in 14 months, but not all cats will go on to develop hyperthyroidism. Although use of cTSH in the
diagnosis of feline hyperthyroidism appears limited, cTSH in combination with TT4 and fT4 may be used to aid in the diagnosis of early hyperthyroidism in cats or hyperthyroid cats with NTI.2 A TT4 concentration within the upper third of the reference range with high serum fT4 and suppressed cTSH is suggestive of hyperthyroidism. For now, cTSH is probably best used to exclude the diagnosis of hyperthyroidism by finding a mid to high normal cTSH in a cat with normal TT4.9

Thyroid scintigraphy

Thyroid scintigraphy provides anatomical and functional information of thyroid tissue. Thyroid scintigraphy is useful in confirming the diagnosis of hyperthyroidism in cats with suspected hyperthyroidism but normal or borderline serum TT4 and fT4 due to either early hyperthyroidism or nonthyroidal illness.11,12 However, there have a few cats with false positive results on thyroid scintigraphy.13 Thyroid scintigraphy can also be used to confirm euthyroidism in cats with false positive TT4 and/or free T4.9,12

Diagnosis of concurrent CKD

Chronic kidney disease (CKD) is also common in middle aged to older cats, with pre-existing kidney disease being present in 14-40% of hyperthyroid cats.14-19 Diagnosis of CKD in cats with concurrent hyperthyroidism can be difficult as increased glomerular filtration rate (GFR) and decreased muscle mass can lower serum creatinine and mask renal dysfunction.1,19-21 Effective renal blood flow increased by 28%, GFR increased by 18%, and creatinine decreased from 1.1 to 0.7 mg/dl after induction of experimental hyperthyroidism in cats.21 Spontaneous hyperthyroidism affects renal function to an even greater degree.14,18,19,22

A subnormal pretreatment GFR in cats with hyperthyroidism may predict the risk of developing post-treatment azotemia.14 Unfortunately, measurement of GFR can be expensive and technically demanding to measure in clinical patients, and is not readily available in most practices. In addition, documentation of a normal GFR prior to treatment does not ensure that a cat will not become azotemia after resolution of hyperthyroidism. Pretreatment creatinine, BUN, and USG are unreliable markers for the development of azotemia.23,24 Currently, there is no biomarker that has been shown to predict the development of posttreatment azotemia in hyperthyroid cats. Markers of tubular dysfunction, such as retinol binding protein, urine protein:creatinine ratio, N-acetyl-β-D-glucosaminidase, have failed to predict the development of post-treatment azotemia.23-26 The current recommendation to evaluate the effects of restoration of euthyroidism on renal function involves a therapeutic trial with methimazole. The ability to use
a single pretreatment blood test for the prediction of post-treatment azotemia would be clinically valuable. Further studies are needed to see if SDMA holds such promise.

Management of Hyperthyroidism

Once a diagnosis of hyperthyroidism is confirmed appropriate treatment must be initiated. There are four different types of treatment currently available for feline hypothyroidism. These include radioiodine therapy, surgical thyroidectomy, antithyroidal drugs, and iodine deficient diets. Each treatment has advantages and disadvantages and treatment should be tailored based on the individual patient and owner.

Antithyroidal drugs

Methimazole can be used for long-term management of hyperthyroidism, as a trial to evaluate renal function, or for stabilization prior to surgical thyroidectomy. Methimazole is effective in up to approximately 90% of hyperthyroid cats.\(^1,27\) Methimazole is readily available, inexpensive, can be administered orally or as a transdermal formulation, and the effects on thyroid function are reversible with discontinuation of the medication. Side effects are rare but can occur in up to 18-25% of cats which include blood dyscrasias, hepatopathy, vomiting, and facial excoriations.\(^1,28\) Adverse effects typically occur within the first month of treatment and rarely occur > 3 mo after treatment. Methimazole does not block the release of preformed hormones and it takes up to 2-3 weeks before a response may be seen. Frequent monitoring is recommending while on methimazole to ensure control of hyperthyroidism while avoiding hypothyroidism, monitor for adverse effects or toxicity, and monitor for the development of renal disease.

Methimazole is not curative as it inhibits the production of thyroid hormones but does not remove or slow growth of the thyroid tumor. Some cats may develop refractory hyperthyroidism to methimazole therapy which may be due to progression to a large thyroid tumor or transformation to carcinoma leading to decreased efficacy of the drug.\(^29,30\)

Cats that have azotemia at the time of diagnosis should be treated with initial lower doses of methimazole (1.25 mg q 24hr) with the dose slowly titrated to effect to avoid signs of overt renal failure while also avoiding iatrogenic hypothyroidism. One study found up to 20% of cats on methimazole had iatrogenic hypothyroidism.\(^31\) Cats that develop worsening azotemia or new azotemia while on methimazole that have a low to low normal T4 should have cTSH performed to evaluated for iatrogenic or subclinical hypothyroidism and the dose of methimazole adjusted.\(^31,32\)
Surgical Thyroidectomy

Surgical thyroidectomy is an effective, curative therapy in most cases and only requires a short hospital stay pending no complications. With radioiodine therapy becoming more readily available, this technique is becoming less common. Complications include perioperative mortality, laryngeal nerve damage, hypothyroidism, hypoparathyroidism and recurrence.1,27

Radioiodine Therapy

Radioiodine therapy is the treatment of choice as it is curative, noninvasive, and has minimal risks. Radioiodine is highly effective in 95% of cats with one treatment. It offers an alternative to owners who cannot medicate their cats or cats that cannot tolerate methimazole or fail to respond to methimazole or nutritional management. It also avoids the risk of anesthesia and surgery. The disadvantages to radioiodine therapy include the risk of permanent hypothyroidism, up-front costs, requirement of special facilities and isolation period during and after treatment. A withdrawal period of methimazole or y/d is required by most facilities prior to treatment. At the VTH we require patients be off methimazole or low-iodine diet at least 2 weeks prior to their appointment. This allows enough time for hypothyroid state to return and suppress TSH. This will limit the uptake of radioactive iodine in normal thyroid tissue to lessen the risk of iatrogenic hypothyroidism.12

Follow-up monitoring to evaluate thyroid function and development of azotemia is recommended, typically at 1 mo, 3 mo, and 6 mo. Radioactive iodine therapy currently costs $1,500 at the VTH. This includes pretreatment screening (CBC, Chemistry, UA, urine culture, T4/TSH, BP and fundic examination), thyroid scintigraphy, hospitalization, radioactive iodine treatment, and follow up blood work sent to the VTH at 1 mo, 3 mo, 6 mo (recheck fees associated with rDVM visits are not included).

Some facilities recommend a methimazole trial prior to permanent treatment of hyperthyroidism such as with radioiodine therapy. As hyperthyroidism leads to increased GFR and RBF, this can mask preexisting kidney disease. Initiating treatment with methimazole will allow for assessment of renal function once euthyroidism is achieved. GFR decreases up to 1 month after euthyroidism is established, therefore, renal function should be evaluated after 4 weeks of euthyroidism. Unless significant worsening of renal disease occurs or clinical signs of renal compromise occur, treatment will still likely be recommended. It is uncommon for renal disease to progress more than one IRIS stage after treatment of hyperthyroidism.33 More importantly, it has been shown that the development of post treatment azotemia is not
associated with shortened survival compared to nonazotemic cats. Thus, it has been questioned if methimazole treatment is necessary in nonazotemic cats prior to definitive therapy as it is unlikely to change recommendations for treatment. It is most important to perform methimazole trials in cats with azotemia at time of diagnosis to ensure their renal disease does not significantly worsen or clinical signs of overt renal failure develops once euthyroidism is achieved.

**Nutritional Therapy**

Over the past several years, an alternative treatment for feline hyperthyroidism with low-iodine diet (Hill’s y/d) has become readily available. There are only a few studies available evaluating efficacy, and the long-term effects of low-iodine deficient diet are still undetermined. A low-iodine diet works by reducing thyroid hormone production as iodine is important substrate for thyroid hormone synthesis.

This diet has been shown to be effective for lowering serum T4 in hyperthyroid cats. Up to 75-83% of cats will have serum T4 within reference range within 60-180 days. Clinical signs have been noted to improve within 4 weeks of therapy. Cats with higher serum T4 may take longer to respond. The interesting finding with low-iodine diets is that creatinine either decreases or stays stable which is contrast to most other treatment modalities where creatinine increases and some cats developing azotemia. As thyrotoxicosis increases renal blood flow and subsequently GFR, treatment of hyperthyroidism typically leads to a decrease in GFR. One study showed that GFR didn’t significantly decrease within 6 mo in cats treated with low iodine diet, but not all cats became or remained euthyroid throughout the study period. Another study showed that although cats had T4 within reference range, bodyweight and tachycardia failed to improve indicating that hyperthyroidism may not be well controlled. There are other factors that could have led to these finding such as nonthyroidal illness. Further long-term studies (> 1 year) on the effectiveness of low-iodine diet, effects on renal function, and effects of iodine deficiency are needed.

Currently, a low-iodine deficient diet appears effective at lowering T4 concentrations in hyperthyroid cats and may be best suited for cats with mild to moderate hyperthyroidism. This is an attractive option for cats who may not tolerate oral or transdermal methimazole and who are not deems safe to undergo radioiodine therapy or surgical thyroidectomy or owners who decline such treatments.

**Concurrent CKD in hyperthyroid cats**
Hyperthyroidism may contribute to progression of kidney disease; although, there is no direct evidence that hyperthyroidism leads to chronic kidney disease or kidney damage in cats. Markers of tubular injury, retinol binding protein, urine protein:creatinine ratio, N-acetyl-β-D-glucosaminidase, are increased in hyperthyroid cats and decreases or normalized with treatment indicating that hyperthyroidism is responsible for the kidney injury.21-38

Hyperthyroidism can lead to renal hypertension leading to glomerulosclerosis, and, thus progression of CKD.27 Since there is some evidence that hyperthyroidism may contribute to CKD, it is not recommend to keep cats slightly hyperthyroid for the sole purposes of normalizing or decreasing serum creatinine.

References


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