Feline Hyperthyroidism

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Feline hyperthyroidism is a multisystemic disorder arising from excess production of the active thyroid hormones (triiodothyronine [T3] and/or thyroxine [T4]) from an abnormally functioning thyroid gland. Approximately 97-99% of cases result from benign nodular hyperplasia, adenomatous hyperplasia or adenoma of the thyroid gland.

The autonomous secretion of T4 and T3 produces a negative feedback effect on the pituitary gland, suppressing the release of thyroid-stimulating hormone (TSH) such that any normal thyroid tissue atrophies. In 70% to 75% of cats with hyperthyroidism, both thyroid glands are affected. Only 1% - 3% of cases are caused by malignant thyroid carcinoma. Hyperthyroidism is seen mainly in middle-aged to older cats, with the age at presentation ranging from 4 to 23 years (mean of 13 years). Only 5% of hyperthyroid cats are younger than 10 years at time of diagnosis. There is no sex or breed predisposition, although Siamese and Himalayan (colour-point Persian) cats seem to be under-represented in some studies.

Incidence and Risk Factors
The worldwide incidence of feline hyperthyroidism has steadily increased since the early 1980s and it is now one of the more frequently diagnosed disorders in small animal practice. Despite an increase in incidence however, the exact cause of the disease is still unknown. A number of theories have been proposed involving factors related to diet (possibly including the presence of goitrogens, eating canned cat food, iodine content, or frequent food changes), environmental causes (possibly associated with cat litter, environmental toxins, pollution, or exposure to allergens), a genetic mutation, abnormal immune responses, or altered hormonal responses.

Several substantial epidemiological studies from the USA, UK, Hong Kong and New Zealand have revealed some contradictory results, but also some common risk factors.

These include an increased risk in indoor cats, female cats, cats in multi-cat households, cats with dental disease (independent of age), use of topical flea preparations and pesticides, use of cat litter (not linked to increased risk in indoor cats), consumption of certain flavours of canned foods (fish or liver and giblet flavour) and increased risk in non-pure bed cats.
Clinical signs
The clinical signs of hyperthyroidism vary in severity and cats diagnosed earlier these days and so often show less of the classic clinical signs. The disease is insidiously progressive and owners may consider signs, especially when mild, part of the ‘normal’ aging process. Thus months may pass before veterinary care is sought.

General features of the disease include:
• Weight loss (one of the most common clinical signs and seen in more than 80% of cats with the disease)
• Hyperactivity
• Polyuria and polydipsia
• Unkempt hair coat
• Cardiovascular signs (very commonly seen) including tachycardia, heart murmurs, gallop rhythm, increased apical pulse, evidence of systemic hypertension (e.g. retinal detachment), left ventricular hypertrophy seen on echocardiography and evidence of congestive heart failure (e.g. dyspnoea, pulmonary crackles in cats with pulmonary oedema and/or pleural effusion)
• Palpable goitre
• Gastrointestinal signs such as polyphagia or anorexia (seen in apathetic hyperthyroidism), vomiting and less commonly diarrhoea
• Muscle weakness and atrophy (rarely seen)

Cats showing depression, lethargy and reduced appetite are referred to as apathetic hyperthyroid cases and have traditionally accounted for less than 10% of all hyperthyroid cases. Some of these cats are overweight rather than thin and most of them are suffering from either severe cardiac complications associated with their hyperthyroidism or have underlying neoplastic disease.

The overwhelming majority of hyperthyroid cats have a palpable goitre. Increasingly however, cats with ‘cold’ thyroid nodules have been identified (i.e. the presence of palpable thyroid nodules without detectable hyperthyroidism). Many of these cats are in fact suffering from subclinical hyperthyroidism. It is now thought that most hyperthyroid cats go through a 1-3 year period of subclinical hyperthyroidism before developing overt hyperthyroidism. During this period, the cat has a total plasma T4 concentration within the normal reference range in combination with persistently low levels of TSH (< 0.03 ng/ml). Many of the cats later go on to develop hyperthyroidism, so close monitoring of these patients is justified.

Diagnosis
As hyperthyroid cats are being diagnosed earlier, when showing fewer clinical signs than in the past, there has been a change in clinical emphasis. Instead of simply confirming a diagnosis in a cat presenting with the classical clinical signs the goal is now to diagnose hyperthyroidism in cats with few, if any, clinical signs or ruling out the disease in cats presenting with varied problems that may or may not be related to hyperthyroidism.

General screening laboratory tests, diagnostic imaging (echocardiography, radiography) and electrocardiography may provide supportive evidence of hyperthyroidism or detail the extent of cardiac involvement. Screening laboratory tests are also useful in eliminating other diseases with similar clinical signs or in depicting concurrent disorders potentially masked by hyperthyroidism that may be important in treatment decisions and ultimate prognosis, such as the presence of chronic renal disease, diabetes mellitus or neoplasia.

Changes found on routine screening tests include:
• Elevated liver enzyme activities (alanine aminotransferase (ALT) and alkaline phosphatase (ALP). At least one of these liver enzymes is elevated in 90% of hyperthyroid cats.
• Leukocytosis, eosinopenia and erythrocytosis
• Mild hypokalaemia and hyperphosphataemia, in the absence of azotaemia, are also seen in a small number of affected cats
• Hyperthyroid cats have also been shown to be more vulnerable to bacterial lower urinary tract infections, with a prevalence of 12% in one study, so cystocentesis and urine culture is indicated. Urinalysis is also indicated as part of detailed screening for concurrent illnesses such as chronic kidney disease and diabetes mellitus.

In most cats, the diagnosis can be confirmed by measuring resting serum total thyroxine levels (T4). Serum T4 concentration includes both the protein-bound and free levels of T4 circulating in the blood and in most cats, hyperthyroidism can be diagnosed on the basis of high resting serum T4 concentration (T4 > 50nmol/L). Measurement of serum total T3 (tT3) alone is not usually recommended because it is less sensitive than measuring T4 (about 30% of hyperthyroid cats have normal tT3 values). Occasionally normal resting serum T4 concentrations are recorded for cats with hyperthyroidism. This could be due to within or between day variations in mildly affected animals or the effects of concurrent non-thyroidal illness.

If hyperthyroidism is suspected despite a normal, albeit high, T4 concentration (T4 30-50 nmol/L), there are a number of possible investigative options:

Retest the T4
In cats in which overt, manageable underlying disease is identified, such concurrent disease should
be first managed before proceeding with further thyroid testing. Once concurrent disease is resolved, the “euthyroid sick effect is removed” and most hyperthyroid cats will develop a clearly high tT4, confirming the diagnosis. Conversely, in cats without any overt underlying disease, simply repeating the serum tT4 concentration after 2 weeks may be diagnostic if the tT4 is fluctuating in and out of the reference interval. In some cats with pre-clinical disease, it may take a number of weeks or even months for the serum tT4 concentrations to increase into the range diagnostic for hyperthyroidism.

Test serum free T4
In cats with mild hyperthyroidism and tT4 values within the upper third of the reference interval, serum free T4 (fT4) concentrations can also aid in diagnosis. Serum fT4 concentrations are more consistently elevated (less fluctuation) in hyperthyroid cats than are tT4 concentrations.

Although fT4 is more sensitive than tT4 for diagnosing hyperthyroidism, the test specificity for fT4 is poor, with up to 20% of sick (and some clinically normal) euthyroid cats having false-positive fT4 results. Caution is therefore advised in using serum measurements of fT4 as the sole diagnostic test for hyperthyroidism. As a thyroid function test, fT4 should always be interpreted with a corresponding T4 measurement. A T4 value within the upper third of the reference range (30-50 nmol/L), combined with a high fT4 concentration, is consistent with mild hyperthyroidism, whereas a low or low-normal T4 with a high fT4 is usually associated with non-thyroidal illness.

Serum fT4 is currently measured by one of two methods: Radio-immuno assay (RIA) using kits designed for use in humans and a modified equilibrium dialysis (MED) technique. The MED technique is the most accurate method for determining serum fT4 concentrations but unfortunately is not available in South Africa.

Test serum cTSH
The use of canine TSH (cTSH) assays in cats has recently received attention in the diagnosis of feline hyperthyroidism. A reference range for cTSH of 0.03-0.15 ng/ml has been defined for older cats.

In cats with subclinical and occult hyperthyroidism, cTSH levels are low or undetectable. Therefore if tT4 levels are in the upper half of the reference range (>30 nmol/L) and cTSH levels are low or undetectable (< 0.03 ng/ml), hyperthyroidism can be diagnosed.

A recent study evaluating the usefulness of cTSH as a diagnostic test for feline hyperthyroidism using thyroid scintigraphy as the gold standard, concluded that measurement of serum cTSH concentration is a very sensitive, but nonspecific, diagnostic test. Approximately 98% of hyperthyroid cats had serum cTSH concentrations that are suppressed below the limit of quantification (<0.03 ng/ml), but approximately 30% of the older euthyroid cats in that study also had undetectable serum cTSH concentrations.

The current commercial cTSH assay cannot accurately measure the very low concentrations needed to clearly distinguish between the low-normal serum cTSH concentrations found in some euthyroid cats from the truly low or totally suppressed concentrations found in most hyperthyroid cats. It was shown that combining serum cTSH with tT4 or fT4 concentrations lowered the test sensitivity of cTSH from 98 to 97%, but markedly increased overall test specificity (from 69.9 to 98.8%).

The conclusion reached was that testing in parallel by combining serum cTSH concentration with either tT4 or fT4 concentrations improved the ability to correctly differentiate hyperthyroid cats with occult or mild disease from euthyroid cats suspected of having thyroid disease, especially when serum concentrations of tT4, T3, or fT4 were within the upper limits of their reference interval or only marginally increased.

Dynamic thyroid tests
Other options for diagnosis of suspect cases include dynamic thyroid tests (T3 suppression, TSH/TRH stimulations tests) and thyroid imaging (scintigraphy, ultrasound and CT). Dynamic thyroid tests are not always straightforward to interpret and are much less frequently performed since they require multiple samples to be collected and may result in side-effects.

Thyroid Imaging
Scintigraphy is performed to determine whether there is increased activity in the thyroid glands relative to the activity in the salivary glands 20-60 minutes after intravenous or subcutaneous injection of pertechnetate. It is a very accurate and reproducible test used to differentiate between cats with unilateral or bilateral disease and to check for the presence of ectopic thyroid tissue not palpable in the neck. This is extremely helpful when planning surgery. However as it requires access to specialist facilities, it is not routinely available.

Ultrasonography has been used to document the dimensions and volume of the thyroid glands in euthyroid and hyperthyroid cats and has been shown to have 85.7% agreement with scintigraphy in defining normal and abnormal thyroid lobes. However, it is technically demanding and very operator dependent. CT has been used to determine the dimensions and volume of thyroid tissue in clinically normal cats;
however the value of such imaging in the diagnosis of hyperthyroidism remains undocumented. Although both CT and ultrasonography can provide information regarding thyroid volume and morphological information, including invasiveness and can guide sampling, they are unable to provide functional information and may not identify ectopic thyroid tissue or metastatic disease.

When investigating a cat for possible hyperthyroidism, it is also important to consider all possible differential diagnoses and to look for evidence of multiple interacting diseases. This is because hyperthyroidism is seen most commonly in older cats and this group of patients is often affected by more than one disorder. Diabetes mellitus, renal disease, malassimilation syndromes (including inflammatory bowel disease, early intestinal lymphosarcoma, pancreatitis, and exocrine pancreatic insufficiency), acromegaly, and hyperadrenocorticism are perhaps the most important differential diagnoses.

Treatment
Spontaneous remission of hyperthyroidism has not been reported and prevention is not possible as the aetiology still remains elusive. Because of the benign nature of the thyroid lesions, if treated appropriately, hyperthyroidism carries a favourable prognosis. Failure to institute therapy will result in insidious progression of clinical signs to emaciation, severe metabolic and cardiac dysfunction and ultimately death.

Treatment options include medical management with anti-thyroid drugs, surgical thyroidectomy, thyroid ablation using radioactive iodine (the gold standard in human medicine) or most recently, feeding an iodine-restricted diet. Each treatment option has its own advantages and disadvantages. Selecting one therapy over the other depends on the age of the cat, severity of thyrotoxicosis, presence of concurrent illnesses, facilities available, potential complications, costs and the owner’s lifestyle and willingness to accept the form of treatment advised. There are a few studies directly comparing the outcome of each of the treatment methods available.

One study of 167 hyperthyroid cats suggested that the median survival time (MST) in cats treated with radioactive iodine was significantly longer (4 years) compared with that of cats treated with anti-thyroid drug therapy alone (2 years). Owner/cat compliance and adverse drug reactions play a significant role in this shorter survival time. Pre-existing renal failure also adversely affects survival irrespective of treatment type and results in a MST of about 6 months.

Before deciding which treatment to use, the cat should be assessed for concurrent disease, especially renal disease, systemic hypertension, and heart disease, all of which occur commonly in association with hyperthyroidism. It is particularly important to assess the cat’s renal function (check blood urea nitrogen [BUN], creatinine concentrations, serum SDMA levels and urine specific gravity). This is because resolution of the hyperthyroid state often is associated with an increase in BUN and creatinine concentrations and a decrease in glomerular filtration rate (GFR) and effective renal blood flow. Because of this, some cats without prior evidence of renal insufficiency or with only mild renal impairment develop signs of uraemia after treatment for hyperthyroidism. To determine what effect resolving the hyperthyroid state may have on renal function, a short course of medical therapy is recommended before considering radiotherapy or surgery. Cats which show significant azotaemia should then be maintained on medical therapy and should not be considered suitable candidates for radiotherapy or surgery. Similarly, cats which develop significant azotaemia after radiotherapy or surgery should be given L-thyroxine to maintain a euthyroid or mild hyperthyroid state.

Interestingly in a recent study that compared the survival of cats that developed mild azotaemia (> 177 nmol/L) with cats that did not develop azotaemia following medical therapy, no difference was found between the two groups. These results suggest that the importance of the mild azotaemia that commonly develops after treatment for hyperthyroidism may have been overemphasized previously and does not change long-term outcomes in these cats. The same study however did find that in cats that were inadvertently over-treated and made hypothyroid, the development of azotaemia was of significance as it negatively affected prognosis.

Medical Management
Medical management entails the use of anti-thyroid drugs. It is used in cats for long term control and is advised prior to surgery to decrease the metabolic and cardiac complications associated with anaesthetising hyperthyroid cats and to control clinical signs in cats awaiting radioactive iodine therapy.

Drugs of the thiurylene class, mainly methimazole and carbimazole, are most frequently used for both the pre-operative and long term medical management of hyperthyroidism because of their consistent and potent effect in lowering thyroid hormone concentrations. Methimazole and carbimazole are antithyroid drugs that block T3 and T4 synthesis. They share the same mechanism of action; carbimazole is almost entirely broken down to methimazole in vivo (carbimazole, 5 mg, is broken down to methimazole, 3 mg). It usually takes 1 week of treatment to achieve a significant decrease in T4 concentration.

The dose for both drugs is 2.5 to 5.0 mg per cat administered orally every 12 to 24 hours initially, increasing to every 8 to 12 hours as necessary, adjusted to maintain a euthyroid state, and given for the rest of the cat’s life. The drugs are most effective given twice
or three times daily. The dose should initially be low (especially when renal insufficiency is suspected), and the renal values should be monitored as the dose is gradually increased. When cat and owner compliance is good, the successful response rate is approximately 85%.

Difficulty in administration causes many treatment failures. In an attempt to make medicating simpler, many clinicians are now using topical transdermal applications of methimazole, and initial studies seem to show promise. Advantages of medical therapy are numerous, including easy implementation, no requirements for special facilities, good availability and a reasonable cost to the client. Almost all cats are potential candidates and very few contra-indications, other than presence of thyroid carcinoma, exist.

The main disadvantages of medical therapy in this species, is the high degree of owner and patient compliance required and the rapid recurrence of signs if compliance is lost. In addition adverse and serious side effects occur in about 8-15% of cats treated with carbimazole or methimazole, which may require complete drug withdrawal. The most common is vomiting, anorexia and depression. Blood dyscrasias, facial excoriation, hepatotoxicity, renal decompensation, coagulation abnormalities, generalised lymphadenopathy and even acquired myasthenia gravis occur less commonly. These side effects normally occur within the first 3 months of treatment.

Other medical treatments available include the use of iopanoic acid and beta blockers. The results of studies evaluating the efficacy of cholecystographic agents such as iopanoic acid, in the treatment of feline hyperthyroidism have been disappointing and the drug is not recommended for long term management of the disease but may be suitable for short-term management prior to surgery or radioiodine therapy. Beta blockers such as propanolol and atenolol as well as potassium iodate have also been used successfully in pre-surgical stabilisation but longer term studies are required to evaluate their use for long-term medical management.

Control of hyperthyroidism by percutaneous injection of ethanol into solitary thyroid nodules as well as ultrasound-guided thyroid radio-heat ablation has been described in a small number of cats, but these techniques have been associated with serious side-effects and are unlikely to be a viable option for the majority of hyperthyroid cats.

**Surgical Thyroidectomy**

Surgical thyroidectomy is highly effective, almost always curative and widely available for cats, but the procedure can be associated with significant morbidity and mortality. Hyperthyroid cats also represent an anaesthetic risk due to the systemic effects of the disease. The most common serious post-surgical complications in cats include hypocalcaemia, due to hypoparathyroidism when the parathyroid glands are inadvertently removed, laryngeal paralysis, voice changes and Horner’s syndrome. Treatment failure can occur due to inappropriate unilateral thyroidectomy where there is bilateral disease, incomplete removal of tissue or less commonly the presence of hyper-functional ectopic thyroid tissue. This can be avoided by performing thyroid scintigraphy pre-operatively.

**Radioactive Iodine Treatment**

Radioactive iodine treatment, the therapy of choice in human toxic nodular goiter, is also successfully used in the cat. It is simple, safe and effective and is possibly the best curative treatment for most hyperthyroid cats. Permanent hypothyroidism is rare as is recurrence after successful treatment and other side effects are minimal. The main disadvantages of such treatment are that it is potentially extremely hazardous to personnel, requires prolonged hospitalisation, is costly and is only available in a limited number of centres.

**Iodine Restricted Diet**

A novel option for treatment of feline hyperthyroidism now exists in the form of a commercially available iodine restricted diet (Hills Y/D®). An iodine restricted food was developed based on the hypothesis that feline hyperthyroidism can be managed nutritionally by limiting the amount of dietary iodine available for production of thyroid hormones. Feeding an iodine restricted food has been shown in multiple feeding trials over the past 10 years, in over 100 cats with naturally occurring disease, to decrease thyroid hormone concentration and alleviate clinical signs of hyperthyroidism.

Three additional studies documenting the safety and efficacy of iodine restricted food as the sole therapy of hyperthyroid cats showed that a food with iodine levels at or below 0.32 ppm per dry matter basis was able to convert 90% of the hyperthyroid cats in the study to a euthyroid state within 8-12 weeks. In all these studies biochemical features of renal function remained stable and no other biochemical abnormalities were observed. The only drawback in using an iodine restricted diet is that feeding compliance has to be 100% for the diet to have an effect. Any exposure to products or foods containing iodine, such as compounding agents for medications, treats, supplements, cleaning agents, other pet food, prey food or home prepared meals or treats and even in some cases municipal water, should be discontinued.

The diet has been shown not to have any adverse effects if fed to healthy cats and as such, the maintenance of normal thyroid concentrations and lack of clinical signs of hypothyroidism in these cats indicates that adequate amounts of iodine is provided to healthy animals fed the diet.

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**CPD ACCREDITED ARTICLE**
Prognosis
Without treatment, cats with hyperthyroidism usually die of concurrent renal disease, heart disease, liver disease, or systemic hypertension. With treatment, the prognosis varies from extremely good to guarded, dependent on the presence of heart disease, renal disease, and systemic hypertension; whether or not any systemic damage has become permanent before treatment of the hyperthyroidism; and which treatment options are available. On average, the mean life expectancy of treated cats is approximately 2 years.

References available on www.vet360.vetlink.co.za

Practitioners should be know which assay techniques are being used by their commercial or in-house laboratories.

Serum tT4 can now be measured in five different ways.

- Radioimmunoassay (RIA) has long been considered the gold standard but regulations regarding radioactivity, and the lack of automation have resulted in very few major commercial veterinary laboratories using it apart from diagnostic laboratories within veterinary university hospitals and research facilities.
- Chemiluminescent enzyme immunoassays (CEIAs) (eg, Immulite Total T4 assay and Canine Total T4 assay; Siemens Healthcare) utilise the same type of antibody testing as RIA; however, instead of measuring a radioactive isotope bound to the hormone, this method counts light emissions. The CEIA methodology, which has been validated for use in the cat. South African animal laboratories use this method. However, it is important to be aware that Immulite consists of more than one type of Technology: Immulite 1000 and 2000/XPI, and that there are both ‘human’ and canine versions of the Total T4 assay that can be used.
- A point-of-care enzyme-linked immunosorbent assay (ELISA) test kit is also commercially available for in-house use on feline serum and offers a cost-effective way to determine serum tT4 immediately in house.
- A homogeneous enzyme immunoassay (EIA) method for serum tT4 determination (eg, DRI hyroxine Assay; Microgenics) is now being used by many commercial veterinary laboratories. Like the CEIA and ELISA techniques, this EIA method has been validated for use in the cat and dog.
- Other chemiluminiscence or enzyme immunoassay equipment (eg, Cobas, Roche Diagnostics, Architect System; Abbott Laboratories, ADVIA Centaur, Siemens Healthcare) can be used together with the appropriate human T4 kits.

Most of these human kits have not been validated for use in cats or dogs. In addition, a major limitation of these human assays is the lack of sensitivity and poor performance, especially when attempting to measure the lower tT4 concentrations found in cats.

The correlation of serum tT4 concentrations provided by all of these assay methods is generally good, with the exception of the human T4 kits, which are never recommended, no assay has 100% test sensitivity and specificity. Compared with RIA (the gold standard), CEIA has been shown to provide very similar test results whereas the in-house ELISA methods appear less reliable and have been shown to overestimate the tT4 concentration. When results of the two methods, used in 50 cats, were categorised (low, borderline low, normal, borderline high or high), they were discordant in up to 28 (56%) of the samples.

In samples from 100 cats, with a wide range of expected tT4 values, 60 with untreated hyperthyroidism and 40 which were being monitored after treatment with radioiodine, tT4 was measured both by EIA and CEIA. The results were compared and tT4 values obtained by each method were significantly correlated (R = 0.97; P <0.001). But 11 cats with untreated hyperthyroidism had normal tT4 values when measured by EIA but had clearly high tT4 concentrations when measured by CEIA. Overall, when results of the two methods were categorised (ie, low, normal or high range), serum T4 values were discordant in 16 (24%) of the 66 cats.

The bottom line is that no matter what assay method is used for tT4 measurement, there is the potential for false-negative and false-positive results. Therefore, serum T4 results must always be interpreted in the light of the cat’s history, clinical signs and other laboratory findings.


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