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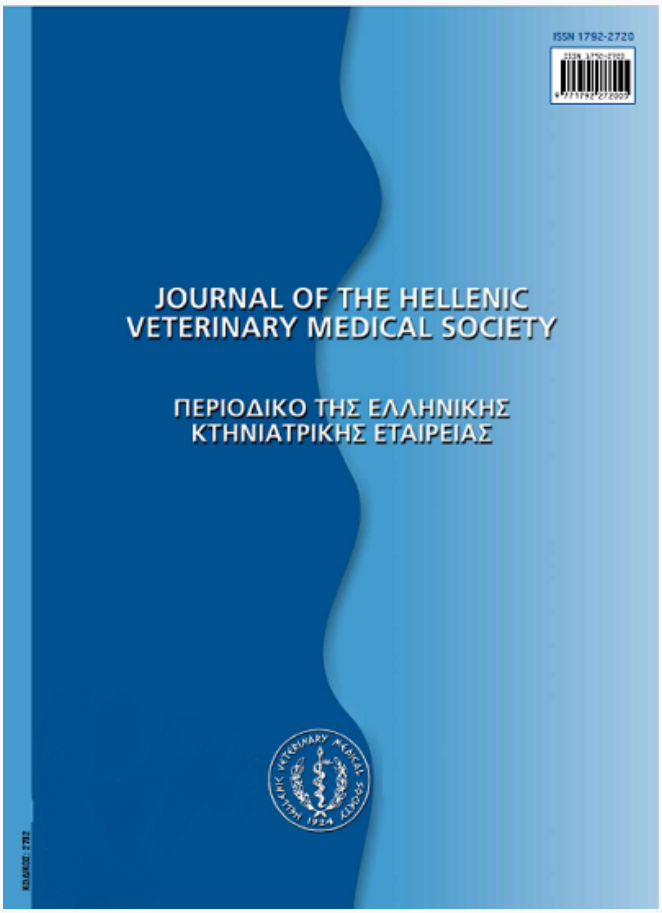

Feline hyperthyroidism: diagnosis and treatment

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Review article
Ανασκόπηση

Feline hyperthyroidism: diagnosis and treatment

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Ο υπερθυρεοειδισμός στη γάτα: διάγνωση και θεραπεία

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ABSTRACT. Hyperthyroidism is a common endocrinopathy in cats older than 8 years, with no sex or breed predisposition. Benign adenomas and adenomatous hyperplasia of the thyroid gland is observed in the majority of cases. Symptoms reflect the effect of thyroid hormone excess in various systems, with weight loss, polyphagia, polyuria-polydipsia, cardiovascular and gastrointestinal abnormalities being common clinical manifestations. On clinical examination, there is frequently prominent thyroid enlargement. Common laboratory abnormal findings include increased activity of alkaline phosphatase and alanino-aminotransferase, hyperphosphataemia, azotaemia and decreased concentration of ionized calcium and creatinine. Definite diagnosis of the disease is based on the demonstration of increased blood concentration of thyroid hormones. Measurement of thyroxine concentration, alone or in conjunction with concentration of free thyroxine, is usually sufficient to reach a diagnosis. When diagnosis is uncertain, thyroid stimulating hormone, scintigraphy and dynamic function tests can be used. The possibility of concurrent diseases (e.g., renal failure, diabetes mellitus) must be investigated, as their presence has implications on diagnosis and treatment. Medical therapy, thyroidectomy, radionine therapy and low iodine diet are also valid options for treatment. Each has advantages and disadvantages that a clinician must take into consideration before instigating treatment. Prognosis for hyperthyroidism is favourable if no severe disease exists concurrently.

Keywords: cat, hyperthyroidism, methimazole, thyroxine.

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ΠΕΡΙΛΗΨΗ. Ο υπερθυρεοειδισμός είναι συχνή ενδοκρινοπάθεια σε γάτες ηλικίας μεγαλύτερης των 8 ετών και οφείλεται σε καλοήθη αδενώματα ή αδενωματώδη υπερπλασία του θυρεοειδή αδένα. Οι κλινικές εκδηλώσεις της νόσου είναι αποτέλεσμα της υπερλειτουργίας του θυρεοειδή αδένα, συχνότερα δε παρατηρούνται κακή θρεπτική κατάσταση, πολυφαγία, πολυουρία-πολυδιψία και συμπτώματα από το πεπτικό σύστημα ή/και το καρδιαγγειακό σύστημα. Στην πλειονότητα των περιστατικών, ο αδένας είναι ψηλαφητός. Κατά την εργαστηριακή διερεύνηση, συχνά ευρήματα αποτελούν η αύξηση της δραστηριότητας της αλκαλικής φωσφατάσης και της αλανινο-αμινοτρανσφεράσης στο αίμα, η υπερφωσφαταιμία, η αζωθαιμία και η μείωση της συγκέντρωσης του ιονισμένου ασβεστίου και τη κρεατινίνης στο αίμα. Η οριστική διάγνωση βασίζεται στη διαπίστωση της αυξημένης συγκέντρωσης των ορμονών του θυρεοειδή αδένα (μέτρηση της συγκέντρωσης της ολικής θυροξίνης ή/και της ελεύθερης θυροξίνης στο αίμα). Εάν η διάγνωση είναι αμφίβολη, μπορεί να πραγματοποιηθούν σπινθιρογράφημα του αδένα ή/και δυναμικές ενδοκρονολογικές εξετάσεις. Επίσης, πρέπει να διερευνάται η συνύπαρξη άλλων νοσημάτων, διότι η παρουσία τους επηρεάζει τη διάγνωση και τη θεραπεία της νόσου. Οι βασικές θεραπευτικές επιλογές περιλαμβάνουν τη φαρμακευτική αγωγή, τη θυροειδεκτομή και τη χορήγηση ραδιενεργού ιωδίου και διατροφής χαμηλής περιεκτικότητας σε ιώδιο. Κάθε επιλογή έχει πλεονεκτήματα και μειονεκτήματα, τα οποία πρέπει να αξιολογηθούν από τον κλινικό κτηνίατρο για επιλογή της εκάστοτε καλύτερης θεραπευτικής προσέγγισης. Ο υπερθυρεοειδισμός έχει καλή πρόγνωση, εφόσον δεν συνυπάρχουν στο ζώο σοβαρές συστηματικές παθολογικές καταστάσεις.

Λέξεις ευρετηρίασης: γάτα, θυροξίνη, μεθιμαζόλη, υπερθυρεοειδισμός.

INTRODUCTION

Prevalence of feline hyperthyroidism has increased over the last 30 years; the disease is currently a very common endocrinopathy of elderly cats (Peterson and Ward, 2007). Benign adenomas or adenomatous hyperplasia of the thyroid gland are documented as causes of the problem in 98% of the cases, while thyroid carcinomas are rare (Turrel et al., 1988; Naan et al., 2006). Diagnosis is considered to be straightforward in overt hyperthyroidism, but early or mild disease can pose diagnostic challenges, especially when a non-thyroid illness co-exists. History findings, epidemiological information, clinical examination and clinicopathological screening of patients can provide valuable indicators for diagnosis of the disease, although a definite diagnosis can be based only on thyroid hormone evaluation. Various treatment options exist and hyperthyroidism carries a favourable prognosis with early detection and appropriate therapy. Objective of this review is to describe the diagnostic approach and treatment options in feline hyperthyroidism.

HISTORY - EPIDEMIOLOGICAL INFORMATION - CLINICAL SIGNS

The most common history findings, epidemiological information and clinical signs related to cases of feline hyperthyroidism are summarised in Table 1.

History

The reported median age of patients, at the time of diagnosis, is 12 to 13 years (range: 4-22 years), with less than 5% of cases being younger than 8 years of age. No sex or breed of animals predisposition exists for development of the disease (Milner et al 2006). A progressive, mild to severe weight loss coupled with normal to increased appetite, is consistent with feline hyperthyroidism (Peterson et al., 1983; Broussard et al., 1995). Concurrent presence of polyphagia or normal appetite and weight loss is a significant finding that limits differential diagnosis in thin cats (Gunn-Moore and Miller, 2006). Polyuria-polydipsia (PU/PD) is common and may often be the only presenting complaint. Nevertheless, it must be kept in mind that in geriatric cats this is a primary sign of various systemic disorders (Mooney and Peterson, 2004).

Gastrointestinal manifestations of feline hyperthyroidism include intermittent vomiting, diarrhoea, increased volume and frequency of defaecations and steatorrhoea (Peterson et al., 1983; Thoday and Mooney, 1992). Behavioural changes are observed in up to 50% of cats, ranging from nervousness/restlessness, to aggressive or frantic behaviour. Panting, respiratory distress, dermatologic problems and heat intolerance have also been reported (Feldman and Nelson, 2004).

A variant of feline hyperthyroidism is termed 'apathetic hyperthyroidism', occurring in 5-20% of cases of the disease. In such cases, anorexia, weak-

Table 1. Summary presentation of history details and clinical signs reported to be associated with feline hyperthyroidism (compiled from Feldman and Nelson (2004), Baral and Peterson (2012), Peterson (2013)).

History details	
Weight loss	85-95%
Polyphagia	60-75%
Polyouria/Polidipsia	45-60%
Increased activity	30-55%
Vomiting	30-45%
Dyspnoea, tachypnoea, panting	20-35%
Gastrointestinal problems: diarrhoea, increased volume of faeces, steatorrhoea	15-20%
Decreased appetite/activity, weakness	5-10%
Heat intolerance	5%
Clinical signs	
Goitre	80-95%
Poor body condition	60-70%
Hyperactivity	50-65%
Tachycardia	50-60%
Heart murmur	35-55%
Alopecia, unkempt dry haircoat, hair matting	15-30%
Gallop rhythm	15-25%
Aggressive behaviour	10-15%
Increased nail growth	5-10%
Stress intolerance	5-10%
Congestive heart failure	1-2%

ness and lethargy are chief complaints, although a large period of polyphagia and weight loss precedes them (Thoday and Mooney, 1992; Bucknell, 2000). A severe non-thyroid illness, e.g. chronic kidney disease, congestive heart failure and neoplasia, usually co-exists. It is important for the clinician to investigate thoroughly apathetic cases, as nature and severity of a concurrent disease will affect prognosis and therapeutic choices (Feldman and Nelson, 2004).

Clinical signs

General appearance

Hyperthyroid cats are in poor body condition, while muscle weakness with neck ventroflexion has also been described (Nemzek et al., 1994; Peterson, 2013). Hair coat is often unkempt, while alopecia and other dermatologic signs may be present as a consequence of overgrooming (Baral and Peterson, 2012).

Palpable thyroid gland (goitre)

A palpable thyroid gland is present in over 90% of cases of feline hyperthyroidism (Peterson, 2013). Even though, thyroid size and total thyroxine blood concentration are related, it is now agreed that presence of goitre is a poor prognostic indicator for the disease (Ferguson and Freedman, 2006; Borreti et al., 2008). Several studies have demonstrated that thyroid enlargement may also exist in elder euthyroid cats. Some cats eventually develop hyperthy-

roidism, indicating that a subclinical hyperthyroid state exists (Norsworthy et al., 2002a; 2002b). Other possibilities in the differential diagnosis for a feline cervical mass include non-functional thyroid and parathyroid cysts, adenomatous parathyroid hyperplasia, lymphoid neoplasia, salivary mucocoele and dermoid cysts (Norsworthy et al., 2002a; Phillips et al., 2003; Tolbert et al., 2009). In conclusion, even though goitre increases the likelihood of hyperthyroidism, it does not precisely reflect the functional status of the gland. When present in a euthyroid cat, a periodical evaluation of thyroid status should be undertaken (Norsworthy, 2002b).

Cardiovascular manifestations

Tachycardia (>240 beats min^{-1}) and a powerful apex beat are frequently recorded in feline hyperthyroidism. Systolic murmurs, grade I-III/VI, the intensity of which varies with heart rate and gallop rhythm, attributed to dynamic left or right ventricular outflow tract obstruction and rapid ventricular filling respectively, are often auscultated (Broussard et al., 1995; Rishniw and Thomas, 2002; Peterson, 2013).

In contrast to earlier reports, feline hyperthyroidism is now considered to be a rare cause of congestive heart failure. The prevalence of congestive heart failure in hyperthyroidism ranges from 2% to 3%, in most cases reflecting decompensation of subclinical heart disease, due to the increased circulating blood volume of the thyrotoxic state (Syme, 2007). Left-sided cardiomegaly, left ventricular hypertrophy, left atrial and ventricular dilation and increased fraction shortening are common, but subtle and clinically insignificant (Bond et al., 1988, Fox et al., 1999; Connolly et al., 2005). Also, thyroid hyperactivity has a modest but significant effect on circulating natriuretic peptide, which should be taken into account when evaluating elderly cats for primary myocardial disease (Menaut et al., 2012).

Hypertension was cited as a common sequel of hyperthyroidism in older studies (Kobayasi et al., 1990). Today its prevalence is thought to be low and is accepted that false positive results are common due to a susceptibility of hyperthyroid cats to the so-termed 'white coat effect'. Hypertension, when present, is mild to moderate and asymptomatic (Sartor et al., 2004; Henik et a., 2008). When substantial elevation of blood pressure is documented, potential occurrence of concurrent disease must be thoroughly investigated, especially of chronic kidney disease (Reusch and Scellenberg, 2010).

Stress intolerance

Stressful events can have adverse effects in hyperthyroid cats. Respiratory distress, cardiac arrhythmias and shock have all been identified in this context. It is important for a clinician to realise the fragility that accompanies the thyrotoxic state and handle accordingly these patients (Feldman and Nelson, 2004).

LABORATORY TESTS

Complete blood count, blood serum biochemical tests and urine testing are useful in supporting diagnosis, eliminating other diseases with similar clinical signs and investigating the presence of concurrent non-thyroid illnesses.

Complete blood count

Haematologic changes are usually mild and of no clinical significance. Erythrocytosis, macrocytosis and increased numbers of Heinz bodies have been described. Increased number of neutrophils or increased lymphocyte and eosinophil numbers can be expected as leucocyte changes (Peterson et al., 1983).

Blood biochemical tests

Increased activity of alkaline phosphatase and alanino-aminotransferase are described in over 90% of cases (Broussard et al., 1995), correlating well with total thyroxine blood concentration. Nonetheless, no hepatic parenchymal or functional abnormalities are noted and liver enzyme activity becomes normal after induction of euthyroidism (Berent et al., 2007). When marked increases in liver enzyme activity occur in mildly hyperthyroid cats, an investigation for liver disease must be pursued, especially when they persist despite treatment. As bile acids are not affected, their measurement is considered very useful in differentiating hyperthyroidism from primary liver disease (Foster and Mooney 2000).

Hyperphosphataemia, in the absence of azo-

taemia, is reported in 20-43% of hyperthyroid cats (Shiel and Mooney, 2007). Also, ionised calcium and parathormone concentrations were found to decrease and increase, respectively, in a significant number of cats in two studies. These findings indicate that hyperparathyroidism is common in hyperthyroidism, even though it may not be clinically significant (Archer and Taylor, 1996; Barber and Elliot, 1996). Azotaemia is present in about 10% of the cases; an expected finding since chronic kidney disease is also common in elderly cats (Broussard et al., 1995; Plantiga et al., 2005). Less commonly, potassium coagulation parametres, serum folate and cobalamin may be affected (Randolph et al., 2006; Milner et al., 2006; Cook et al., 2011).

Urine testing

Results of routine urine testing, in general, do not provide significant results. Urine specific gravity has a significant variation with values ranging from 1009 to 1050 (Broussard et al., 1995). Proteinuria that decreases after therapy institution, is documented in 30% of animals, but is yet of unknown clinical significance (van Hoek et al., 2009a). Urinary tract infections with no abnormalities suggestive of lower urinary tract disease, can occur in up to 12% of patients, hence bacteriological examination is recommended in all cats with hyperthyroidism (Mayer-Roenne et al., 2006).

TESTS FOR DEFINITE DIAGNOSIS OF THE DISEASE

Measurement of total thyroxine blood concentration

Increased total thyroxine blood concentration is a very specific finding, occurring in up to 90% of hyperthyroid cats and is the preferred screening test for feline hyperthyroidism (Peterson, 2013). However, it is now accepted that, overall, 10% of animals with clinical signs and 40% of animals with subclinical or mild disease have normal total thyroxine blood concentrations (Peterson et al., 2001). Concurrent presence of a non-thyroid illness and thyroid hormones fluctuation are the proposed explanations. False-negative results can be observed in mild cases of the disease, in which total thyroxine blood concentration can be found to be within the middle to high-end of the reference range. This effect is of no diagnostic significance in overt disease, in which severe increases in total thyroxine blood concentration occur (Shiel and Mooney, 2007).

Concurrent non-thyroid illness is identified in up to 30% of hyperthyroid cats with the total thyroxine blood concentration being within the normal reference range. Even though the mechanisms involved are not clearly defined, the lowering effect appears to correlate with the severity and not the type of the disease, with lowest concentrations occurring in the animals with most serious clinical signs (McLouglin et al., 1993; Peterson et al., 2001). Fluctuation of thyroid hormones has been demonstrated by serial measurements of total thyroxine blood concentrations in mildly hyperthyroid cats during a 15 day period (Peterson et al., 1987).

Measurement of free thyroxine blood concentration

Free thyroxine is the non-protein bound fraction of thyroxine and is responsible for its biologic effect. Free thyroxine is increased in approximately 98% of hyperthyroid cats, including 95% of the animals in which total thyroxine blood concentration is within the reference range (Peterson et al., 2001). However, free thyroxine cannot be used as a screening tool for feline hyperthyroidism, since it is also found increased n 6 to 31% of euthyroid cats. Another disadvantage in measuring free thyroxine blood concentration is that valid measurements can only be obtained by equilibrium dialysis, an expensive and not widely available technique (Mooney et al., 1996; Peterson et al., 2001; Wakeling, 2008). Free thyroxine blood concentration must always be interpreted in the context of total thyroxine blood concentration and cannot be used as the sole means for diagnosis. Increased free thyroxine blood concentration, coupled with middle to high reference range total thyroxine blood concentration is suggestive of hyperthyroidism, while increased free thyroxine blood concentration with a decreased total thyroxine concentration is usually associated with non-thyroid illness. As increases in total thyroxine blood concentration are always accompanied by increases in free thyroxine blood concentration, measurement of both in overt hyperthyroidism is of no diagnostic importance (Feldman and Nelson, 2004).

Feline thyroid stimulating hormone

Measurement of thyroid stimulating hormone (TSH) is considered to be a first line diagnostic test for hyperthyroidism in human medicine, because it is suppressed even in mild cases and is not influenced by concurrent disease (Shiel and Mooney, 2007). No commercially available assays specifically for cats are currently available. A canine first-generation assay has been used with controversial results. Even though canine thyroid stimulating hormone has a 96% homology with the hormone in cats, a distinction between normal and undetectable values was not found to be always reliable. Today, the value of thyroid stimulating hormone is limited to the exclusion of the disease when a detectable concentration is measured (Wakeling et al., 2008, Rutland et al., 2009).

Scintigraphy

Thyroid scintigraphy is based on the increased uptake of radionine isotopes (^{131}I, ^{123}I) and technetium by the diseased thyroid gland. Proportion uptake or increased salivary to thyroid gland ratio are used and both indices correlate very well with total thyroxine blood concentration. Scintigraphy is not influenced by non-thyroid illness and can also detect mild cases of hyperthyroidism and ectopic thyroid tissue. On the other hand, the need for sophisticated equipment and skilled personnel, as well as its high cost make it largely unavailable (Freeney and Anderson, 2007; Harvey et al., 2008).

Dynamic thyroid function tests

Dynamic thyroid function tests are nowadays obsolete, as measurement of total thyroxine and free thyroxine blood concentration along with scintigraphy are adequate in reaching a diagnosis in practically all cats under investigation. Their use must be considered only in animals, in which repeated measurements of total thyroxine blood concentration are unrewarding and free thyroxine blood concentration or scintigraphy cannot be performed (Peterson, 2013). Details of these tests are summarised in Table 2.

Table 2. Summary of details of dynamic thyroid function tests that may be performed in cats (Shiel and Mooney, 2007).

	Tri-iodothyronine suppression	Thyroid stimulating hormone response test	Thyrotropin releasing hormone response test
Technical details			
Drug used in the test	Liothyronine	Bovine thyroid stimulating hormone	Thyrotropin releasing hormone
Dose administered	15-25 μg kg^{-1}, every 8 h × 7	0.5 IU kg^{-1} once	0.1 mg kg^{-1} once
Route of administration	oral	intravenous	intravenous
Sampling occasions	0 & 2-4 h after final administration	0 and 6 h after administration	0 and 4 h after administration
Molecule assayed	Free thyroxin	Free thyroxin	Free thyroxin
Interpretation of results			
Diagnosis of euthyroidism	<20 nmol L^{-1} >50% suppression	100% increase	>60% increase
Diagnosis of hyperthyroidism	>20 nmol L^{-1} 35% suppression	No increase or minimal increase	<50% increase

HYPERTHYROID CATS WITH TOTAL THYROXINE BLOOD CONCENTRATION WITHIN THE REFERENCE RANGE

Clinicians should always investigate thoroughly for presence of a non-thyroid illness, in cases in which hyperthyroidism is a primary component in the differential diagnosis, but total thyroxine blood concentration remains within the reference range. Middle to high reference range total thyroxine blood concentrations values in a sick cat are highly suggestive for hyperthyroidism, as thyroid hormones decline in sick euthyroid cats. In the absence of overt disease, measurement of total thyroxine blood concentration can be performed again after two to six weeks, as, in most cases, it would eventually revert outside the reference range. Measurement of free thyroxine blood concentration is also a viable option in both cases, due to its high sensitivity. Infrequently, when repeated measurements of thyroxine and free thyroxine blood concentration fail to demonstrate hyperthyroidism or measurement of free thyroxine blood concentration is unavailable, scintigraphy and dynamic thyroid tests can be used for further investigation (Shiel and Mooney, 2007).

HYPERTHYROIDISM AND CONCURRENT DISEASE

Chronic kidney disease

Hyperthyroidism and chronic kidney disease are both commonly encountered in geriatric cats and their co-existence can present a diagnostic challenge (Lurye, 2006; Plantiga et al., 2005). Chronic kidney disease has a suppressive effect on total thyroxine blood concentration. Moreover, it is established that free thyroxine blood concentration is markedly influenced, with false-positive results being common (Wakeling et al., 2008). Chronic kidney disease is also largely underestimated in hyperthyroid patients. Creatinine concentration decreases in the thyrotoxic state, due to the increased glomerular filtration rate and reduction of total muscle mass. Blood urea nitrogen can be decreased or elevated, as a consequence of increased glomerular filtration rate or increased protein catabolism, respectively (Syme, 2007). Other clinical and clinicopathological hallmarks of chronic kidney disease, e.g. polyuria/polydipsia and hyposthenuria, may also be useless, as they are encountered in both diseases (Graves, 2010). It has been suggested that chronic kidney disease is likely in hyperthyroid patients with small and irregular kidneys or when high-normal creatinine concentrations are accompanied by extreme increases in total thyroxine blood concentration (Syme, 2007). On the other hand, hyperthyroidism must be suspected when polyphagia or normalization of azotaemia is observed in cats that had been previously diagnosed with chronic kidney disease (Feldman and Nelson, 2004).

Diabetes mellitus

Previous studies have documented that approximately 6% of diabetic cats develop hyperthyroidism and *vice-versa* (McLoughlin et al., 1993; Crenshaw and Peterson, 1996). Moreover, these were the most common endocrinopathies occurring concurrently in a retrospective study of feline multiple endocrine diseases and accounted for 77% of all cases (Blois et al., 2010). Besides the clinical similarities, several confounding factors make diagnosis difficult when both diseases develop. Presence of a total thyroxine blood concentration within the reference range in a diabetic cat cannot rule out hyperthyroidism, as previously discussed. On the other hand, hyperthyroidism results in a decrease of serum fructosamine, because of accelerated protein turnover and it cannot be used for diagnostic or monitoring purposes in the diabetic cat (Graham et al., 1999; Reusch and Tomsa, 1999). Regarding treatment, occurrence of hyperthyroidism in a well-controlled diabetic cat results in deterioration of glycaemic control and increase in insulin needs. Treatment of the disease improves insulin resistance and dose must be reduced accordingly to avoid hypoglycemia (Hoenig, 2012).

TREATMENT OF THE DISEASE

Treatment options in feline hyperthyroidism include medical management, thyroidectomy, radioactive iodine (I^{131}) administration and nutritional therapy, all these alone or in conjunction with each other. Each option has advantages and disadvantages that must be taken into consideration when deciding a therapeutic strategy (Table 3).

Table 3. Summary comments of major therapeutic approaches in feline hyperthyroidism (Trepanier, 2007; Peterson, 2013).

Therapeutic approach	Advantages	Disadvantages
Methimazole, carbimazole	Inexpensive and readily available drugs	Requirement for life-long, administration
	Reversible action	No curative effect
	>90% efficacy	Frequent development of adverse reactions
		Commonly, occurrence of relapses of the disease
Radionine	>90% efficacy	High initial cost
	Curative effect	Limited availability
	Requirement for single session	Irreversible action
	Effective in cases of ectopic thyroid tissue	
Thyroidectomy	>90% efficacy	High initial cost
	Curative effect	Requirement for anaesthesia and surgery
		Potential development of post-surgical complications
		Irreversible action
Low-iodine diet	High efficacy	Requirement for life-long, administration
	Readily available	No curative effect
	Reversible action	Inadequate nutritional coverage
		Limited scientific data available at the moment

Treatment and renal function ('the methimazole trial')

Feline hyperthyroidism improves clinical signs and biochemical manifestations of chronic kidney disease through increases in glomerular filtration rate. Approximately 20-25% of feline hyperthyroidism cases without known chronic kidney disease will develop azotaemia, regardless of therapeutic modality, as a result of decline of glomerular filtration rate (Graves, 2010). Increases in serum creatinine concentrations occur in 15-50% of cats after treatment (Adams et al., 1997; Becker et al., 2000,; Slater et al., 2001; Williams et al., 2010). Evaluation of various parametres (urine specific gravity, blood urea nitrogen, creatinine concentration) before treatment are not useful in predicting potential development of post-treatment azotaemia (Riensce et al., 2008). In order to have a 'preview' of renal function in hyperthyroid cats, a therapeutic trial with a reversible form of treatment (e.g., methimazole) is recommended initially.

A recent study showed that glomerular filtration rate markedly declines during the first month after induction of euthyroidism and it remains relatively stable the following five to six months (van Hoek et al. 2009a). Therefore, if azotaemia does not develop after a month of reaching euthyroidism, more permanent means of therapy can be pursued. It must be kept in mind though, that no studies could be found to evaluate this hypothesis and it is possible that, in a given patient, azotaemia can occur after thyroidectomy or radionine therapy, even if the animal was found to be non-azotaemic during the therapeutic trial period (Trepanier, 2007).

Medical management

The use of antithyroid medication is a valid treatment modality with high efficacy and low cost. It can be used for long term management, as a means to assess renal function and for improv-

ing conditions related to hyperthyroidism before thyroidectomy or radionine therapy. On the other hand, it is not a permanent treatment; it requires life-long medication, with increased owner and animal compliance, and has side effects (Feldman and Nelson, 2004). Drugs currently used in this approach are methimazole and carbimazole.

Methimazole

The efficacy of methimazole is >90%, when side effects do not occur. The drug blocks synthesis of thyroid hormones by inhibiting the organification of iodide and the coupling of iodio-thyronines to form thyroid hormones. As it does not inhibit release of the stored thyroid hormones, two to four weeks are needed before total thyroxine blood concentration comes within the reference range (Peterson et al., 1988). Goitre size is not expected to be reduced with medical treatment. Recommended starting dose of methimazole is 2.5-5 mg daily, administered in two equal doses. Other schemes, with increased (up to 15 mg daily) and more frequent dosing are described in the literature, but they are not needed and would probably increase the risk of renal decompensation and potential side effects. Also, once daily administration has been shown to be ineffective and it is not recommended. Symptoms begin to resolve two to six weeks after return to normal of total thyroxine blood concentration. If the response is not adequate, up titration of the dose can be made (Trepanier et al., 2003; Trepanier, 2007).

Adverse reactions occur in up to 18% of cats usually within the first three months of treatment (Peterson et al., 1988). Vomiting, anorexia and lethargy are common, transient and respond to dose reduction (Peterson, 2013). Neutropaenia and thrombocytopaenia are documented in 3 to 9% of cats, whilst aplastic anemia has also been rarely described. Blood dyscrasias resolve one week after discontinuation of methimazole, but may reoccur with re-challenge, making drug withdrawal necessary. Face and neck excoriations, hepatotoxicity, coagulation abnormalities and acquired myasthenia gravis are less commonly observed (3% of treated cats) and also require drug discontinuation (Peterson et al., 1988; Sartor et al., 2004; Weiss, 2006).

A formulation for transdermal administration of the drug, compounded in pluronic lecithin organogel, is also available. Its efficacy is documented to be smaller in comparison to oral administration. Also, no differences were observed regarding side-effects, besides gastrointestinal disturbances, which were decreased with the trandermal formulation. Nonetheless, it is a therapeutic alternative, especially when pill administration is difficult (Sartor et al., 2004).

Monitoring is extremely important in ensuring response to treatment and detecting side effects. It begins after two to three weeks and includes measurement of a complete blood count, alkaline phosphatase, alanino-aminotransferase, blood urea nitrogen concentration and creatinine concentration, along with total thyroxine blood concentrations (Trepanier, 2007). Timing of blood sampling is not a significant factor for total thyroxine blood concentration measurement (Rutland et al., 2009; Borreti et al., 2013). If side effects are noted, the drug should be discontinued and another therapeutic option should be pursued (Luyre, 2006).

The goal for total thyroxine blood concentration is to remain in the lower part of the reference range. When increased concentrations occur, the dose can be increased to 2.5 to 5 mg daily and blood concentrations of thyroid hormones are re-evaluated four weeks later. In the long term, the goal is to find the lower dose that keeps total thyroxine blood concentration within the reference range and the cat free of clinical signs with no adverse reactions. After the initial period, total thyroxine blood concentration, complete blood count and biochemical monitoring should be repeated every three to six months (Peterson, 2013).

Carbimazole

Carbimazole is found to be effective when administered at an initial dose of 2.5 to 5 mg daily, divided in two to three doses. The lower range is preferred initially and dose escalation can be made, based on total thyroxine blood concentration measurement. A sustained release formulation of carbimazole also exists that is efficient when given once daily (Frenais et al., 2009). Even though vomiting and anorexia are less commonly observed than methimazole, there are no studies comparing the adverse reactions of the two drugs. Since methimazole is a derivative of carbimazole, carbimazole administration is not advised if methimazole-associated adverse reactions develop (Trepanier, 2007).

Thyroidectomy

Throidectomy is a highly efficient treatment procedure, in the absence of radionine therapy considered to be the treatment of choice. However, it is accompanied with increased morbidity and mortality, in overt hyperthyroidism. Pre-operative management with anti-thyroid medication is advised to minimise anaesthetic and surgical complications. Surgery can be pursued after euthyroidism has been achieved for one to three weeks. If anti-thyroid medications are not tolerated, nutritional therapy or β-blockers (atenolol, propranolol) can be used for pre-operative preparation. Post-operative complications include iatrogenic hypoparathyroidism, laryngeal paralysis and oedema, Horner's syndrome and haemorrhage (Naan et al., 2006). Relapses, although uncommon, occur due to poor technique or ectopic thyroid tissue. Total thyroxine blood concentration should be monitored thereafter once or twice a year (Peterson, 2013).

Radionine therapy

Radioactive iodine therapy (I^{131}) is the treatment of choice for hyperthyroidism. A single session restores euthyroidism in 95% of cats, while the remaining will respond to a second session. Adverse reactions are rare, but a pre-treatment period with methimazole is considered mandatory. Regardless of the high-efficacy, the need for special facilities and skilled personnel coupled with the high cost makes the procedure of limited availability (Baral and Peterson, 2012).

Reduced iodine diet

Recent studies have concluded that a reduced iodine, commercially available diet led to induction of euthyroidism in a cohort of cats within four to twelve weeks. Even though further research is needed to evaluate safety and efficacy of reduced-iodine diets, indications for their use include cats that cannot tolerate oral medication and are not appropriate candidates for more permanent treatment modalities. Nevertheless, the approach is not curative and requires life-long and exclusive administration; moreover, high carbohydrate, relatively low-protein composition of such diets would not be ideal for elderly hyperthyroid cats with muscle wasting (Melandez et al., 2011; Yu et al., 2011; Peterson, 2013).

POST-TREATMENT AZOTAEMIA

As mentioned earlier, some cats will develop post-treatment azotaemia. In these patients, the goal to maintain euthyroidism with no signs of uraemia is not always feasible. Treatment should be tailored to the individual patient and no established formula or data exist to support recommendations. Clinicians must decide whether to allow a cat to remain thyrotoxic, in order to preserve glomerular filtration rate or not, depending on severity of clinical signs. Interestingly, a recent study in a large population of hyperthyroid cats concluded that development of azotaemia post-treatment did not significantly influence survival of the patients (Wakeling et al., 2006; Williams, 2010).

TREATMENT OF A NEWLY DIAGNOSED HYPERTHYROID CAT WITH PRE-EXISTING AZOTAEMIA

It is important to understand that presence of chronic kidney disease does not exclude treatment for hyperthyroidism. On the contrary, recent evidence suggests that hyperthyroidism contributes to development and further progression of chronic kidney disease with detrimental implications for kidney function in cats with untreated or poorly regulated hyperthyroidism (van Hoek et al., 2009b). Medical, and perhaps nutritional, management is the only viable choice in such animals. Drugs must be introduced gradually at a low starting dose (1.25 mg, once daily) and up-titrated with caution. Inevitably, glomerular filtration rate would decline and chronic kidney disease symptoms will worsen. Subsequent management should be based on clinical response and serum creatinine and blood urea nitrogen concentrations, not on total thyroxine blood concentration, which is unreliable unless it is markedly increased.

Concurrent management of chronic renal failure is also extremely important. Prognosis of hyperthyroid cats with chronic renal failure is guarded to poor, especially when euthyroidism cannot be achieved. In such cases, median survival times reported are approximately 6 months (Syme, 2007; Peterson, 2013).

CONCLUDING REMARKS

Hyperthyroidism is commonly observed in geri-

atric cats with a good long term prognosis. A thorough search for historical and clinical evidence of the disease provides valuable information. The diagnosis is ultimately based on documenting increased blood concentrations of thyroid hormones.

Concurrent non-thyroid illness must be excluded in a diligent manner, as they affect diagnosis and treatment options. Medical management, surgery, radionine and nutritional therapy are widely used therapeutic measures with good results. Close monitoring is essential to achieve a favourable outcome.

CONFLICT OF INTEREST STATEMENT

None of the authors of this article has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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