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Hyperthyroid cats and their kidneys: a literature review

L Yu,[a]* L Lacorcia[a] and T Johnstone[b]

Hyperthyroidism and chronic kidney disease (CKD) are common diseases of geriatric cats, and often occur concurrently. Thus, a thorough understanding of the influence of thyroid function on renal function is of significant value for all feline practitioners. Among other effects, hyperthyroidism causes protein catabolism and increases renal blood flow and glomerular filtration rate (GFR). These effects render traditional renal markers insensitive for the detection of CKD in cats with uncontrolled hyperthyroidism. Furthermore, the development of iatrogenic hypothyroidism with over treatment of hyperthyroidism can be detrimental to renal function and may negatively affect long-term survival. This review discusses important diagnostic considerations of feline hyperthyroidism, as well as key treatment modalities, with an emphasis on the use of radioiodine and the importance of post treatment monitoring of thyroid and renal parameters. In Australia, a common curative treatment for cats with benign hyperthyroidism (i.e. thyroid hyperplasia or adenoma) is a fixed dose of orally administered radioiodine, regardless of the serum total thyroxine concentration at the time of diagnosis. This review discusses the long term outcomes of this standard of care in comparison with current, relevant research literature from around the world. Finally, this review explores the use of symmetric dimethylarginine (SDMA) in assessing renal function before and after treatment in hyperthyroid cats. SDMA correlates well with GFR and creatinine in non-hyperthyroid cats, but our understanding of its performance in hyperthyroid cats remains in its infancy.

Keywords feline hyperthyroidism; radioiodine; I-131; chronic kidney disease; renal azotaemia; symmetric dimethylarginine; SDMA

Abbreviations CEIA, chemiluminescent enzyme immunoassay; CKD, chronic kidney disease; ED, equilibrium dialysis; fT4, free thyroxine; GFR, glomerular filtration rate; IRIS, International Renal Interest Society; NTI, non-thyroidal illness; RI, reference interval; SDMA, symmetric dimethylarginine; TSH, thyroid-stimulating hormone; TT4, total thyroxine; USG, urine specific gravity

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Feline hyperthyroidism

Hyperthyroidism is the most common endocrinopathy affecting middle-aged to geriatric cats.[1,2] In over 97% of cases, the clinical manifestation arises from the development of functional adenoma or adenomatous hyperplasia of the thyroid tissue. Functional thyroid carcinoma, most commonly adenocarcinoma, is seen in the remaining 1%–3% of hyperthyroid cats.[1] Feline thyroid carcinomas are locally invasive with a high propensity for metastasis. Metastatic rates of up to 71% have been documented at necropsy, most frequently to the regional lymph nodes, followed by the lungs.[3] Thyroid carcinomas may be grossly indistinguishable from benign disease by being well encapsulated and mobile with respect to adjacent tissue, and malignancy cannot always be inferred through diagnostic imaging findings, due to possibility of there being ectopic thyroid tissue. Carcinomas may also be clinically indistinguishable from benign disease, though the index of suspicion for thyroid carcinoma increases in cases that become rapidly debilitated, and/or are refractory to standard approaches with medical or definitive treatment.[1,4] Cats with presumptive benign disease controlled with medical management may also require sequential dose escalation, or even become refractory to medical management over time, due to the continual growth adenomatous tissue. A clinical classification scheme using the acronym SHIM-RAD has been proposed to identify cats with severe disease or suspected thyroid carcinoma, without histopathological confirmation.[5] SHIM-RAD stands for hyperthyroid cats with severe, huge, intrathoracic, multifocal disease, refractory to anti-thyroid drugs, and urges the clinician to consider the likely clinical course to guide additional diagnostic and treatment recommendations for this subgroup of cats when histopathology is not available for confirmation. As the prevalence of suspected thyroid carcinomas increase proportionally with disease duration, transformation to malignancy over time has been postulated.[5] In a prospective cohort study of 2096 cats using thyroid scintigraphy to characterise hyperfunctional thyroid tissue in hyperthyroid cats, bilateral disease was most common (60% of cases), while unilateral and multifocal disease (three or more distinct thyroid tumour nodules) were seen in 35% and 5% of cases, respectively.[6]

Since its recognition in 1979, hyperthyroidism has been detected in cat populations worldwide.[1,7,8] The advent of improved animal health care (with the consequent longer life span of cats) and increasing awareness by both owners and veterinary clinicians has meant that feline hyperthyroidism is more frequently diagnosed, and recognised earlier in the disease process in recent years.[9,10] These factors all likely contribute towards an absolute increase in the prevalence of hyperthyroidism reported in cat populations throughout the world.[11–13] In Australia and New Zealand, feline hyperthyroidism continues to be recognised as the most common endocrinopathy of middle-aged to older domestic cats.[8,14] A survey of Australian

*Corresponding author., lucia.yu@vrh247.com.au
[a]Veterinary Referral Hospital, Dandenong, Victoria, Australia; lucia.yu@vrh247.com.au
[b]Animal Referral Hospital, Essendon Fields, 72 Hargrave Avenue, Essendon Fields, Victoria, 3041, Australia

general practice veterinarians published in 2016 found the majority of respondents (95% of N = 546) had diagnosed more than one cat with hyperthyroidism in the previous 6 months.[15]

Pathophysiology of feline hyperthyroidism

Transplantation of feline adenomatous thyroid tissue into murine models demonstrated autonomous cell growth and function that is independent of extra-thyroidal humoral stimulation.[16] Furthermore, somatic mutations in the transmembrane region of exon 10 of the thyroid-stimulating hormone (TSH) receptor gene within adenomas and adenomatous hyperplastic nodules from cats with hyperthyroidism have been identified.[17] However, the trigger for such mutations remains unknown.

Epidemiologic studies looking at risk factors for feline hyperthyroidism commonly conclude that a single factor cannot explain the underlying aetiology of hyperthyroidism.[8,11,12,18,19] Potential environmental exposures to goitrogenic 'thyroid disruptors' such as the ubiquitous flame retardant polybrominated diphenyl ethers in household products, soy isoflavones in feline maintenance diets and bisphenol A used to line metal cans have been associated with the development of feline hyperthyroidism.[18,20,21] It has been postulated that these 'thyroid disruptors' decrease the effective circulating serum thyroid hormone concentration through thyroid hormone receptor inhibition or inhibition of key enzymes required in the production or activation of thyroid hormones in cats. This results in chronic overstimulation of the thyroid tissue by up-regulated TSH secretion as part of the physiologic negative feedback mechanism, with subsequent aberrant hyperplasia of feline thyroid follicular cells.[8]

Variability (excess or deficiency) in dietary mineral content, such as selenium and iodine also have postulated associations with thyroid dysfunction in cats, but as for the aforementioned 'thyroid disruptors', prospective longitudinal studies assessing the association between exposure of the aforementioned substances and feline hyperthyroidism are lacking and a causal link is yet to be established.[20]

In a retrospective epidemiological cross-sectional study, long-haired non-purebred cats were at increased risk of hyperthyroidism compared with shorthaired non-purebred cats and purebred cats.[22] The mechanism underlying these associations has not been established, although it was postulated that there could be an increased requirement for tyrosine for producing pigment, or increased exposure to environmental goitrogens ingested via grooming.[22]

Regardless of the underlying pathology, feline hyperthyroidism results in the overproduction of the hormone thyroxine and, to a lesser degree, tri-iodothyronine in the thyroid gland. Thyroxine is the main circulating thyroid hormone and is highly protein-bound, with less than 1% of thyroxine circulating in the unbound (free) state. In peripheral tissue, only free thyroxine can enter cells to be de-iodinated to tri-iodothyronine, which is three to five times more potent than thyroxine. Thyroid hormones bind to receptors in the nuclei, triggering a series of cascades that ultimately influence gene coding for regulatory enzymes.[1]

Feline hyperthyroidism causes a state of hypermetabolism that affects multiple organ systems. Many of the resultant haemodynamic changes directly or indirectly affect the kidneys.[23] An elevation in tri-iodothyronine has been demonstrated to cause vascular smooth muscle relaxation, thus decreasing peripheral vascular resistance as seen in in-vitro murine models and in hyperthyroid human patients.[24–26] The renin-angiotensin and aldosterone system (RAAS) is consequently activated, as demonstrated in both human and feline hyperthyroid patients.[24,27,28] Thyroid hormones have been shown to increase renin mRNA and renin production in mice models.[29,30] In human hyperthyroid patients, the up-regulation of RAAS has been demonstrated to increase renal sodium resorption within the proximal tubule and loop of Henle to ensure arterial filling volume can be maintained.[24,28] Finally, murine models have demonstrated an upregulation of β-adrenergic receptor expression within cardiac and renal cortical tissues,[31] in-turn enhancing sympathetic nervous system activity and RAAS activation, as described above.[28] Clinically, this manifests as an increased basal heart rate, left ventricular contractility and blood volume in human patients,[26] in turn increasing renal blood flow, glomerular capillary hydrostatic pressure and increased glomerular filtration rate (GFR).[32] It is presumed that feline hyperthyroidism parallels the pathophysiology occurring in human hyperthyroid patients.[23] Ultimately, the combination of artificially elevated GFR and muscle mass dependant serum creatinine commonly results in the masking of chronic kidney disease (CKD), common in this population of cats.[9,33] The complex relationship between thyroid and renal function will be discussed in greater detail in the latter portions of this literature review.

Diagnosis of feline hyperthyroidism

Diagnosis of feline hyperthyroidism requires a combination of clinical history, physical examination findings and specific clinicopathological testing. Thyrotoxicosis and catabolism result in weight loss in the face of a normal to increased appetite. Hyperthyroid cats also can be agitated and vocal, become tachypnoeic and even exhibit open-mouth breathing in the absence of respiratory disease.[1,34] Tachycardia and mild to moderate systolic murmurs are also relatively common, occurring as a result of the aforementioned alterations in cardiovascular hemodynamics.[9,35,36] Finally, polyuria, polydipsia, gastrointestinal signs such as vomiting and diarrhoea and an unkempt appearance complete the classic list of presenting clinical signs in cats with hyperthyroidism.[1,34] Contrary to these classic clinical signs, 'apathetic hyperthyroidism' is historically reported in 10% of hyperthyroid cats, and presents with hyporexia, listlessness and lethargy.[35,36]

Though hyperthyroid cats commonly have palpable thyroid glands, in recent times, the size of most palpable nodules are much smaller (≤5 mm length)[10] than previously described.[9] This physical examination finding in isolation is not specific for the diagnosis of hyperthyroidism as up to 20% of healthy cats and cats with non-thyroidal illness (NTI) were found to have a palpable thyroid gland, and when found in hyperthyroid cats, however, no healthy cats and only 2 (N = 245 cats) with NTI had nodules >5 mm, suggesting increased specificity for diagnosis of hyperthyroidism with larger thyroid nodules.[10]

Most commonly, definitive diagnosis of hyperthyroidism is by demonstration of an elevation in total thyroxine (TT4); the total concentration of bound and unbound thyroxine. In cats with mild disease or those that have concurrent NTI, the TT4 may fall within the upper half of the reference interval (RI).[37] In these cases, repeating TT4 2–4 weeks later is recommended if clinical suspicion for presence of hyperthyroidism remains,[34] though ideally concurrent potential NTI have been excluded or controlled. If the same result is found, measurement of free thyroxine (fT4); the unbound and biologically active fraction of the T4 hormone, would be recommended.

Free T4 is more sensitive for the diagnosis of hyperthyroidism than TT4; up to 95% of hyperthyroid cats with normal TT4 may have an elevated fT4 concentration.[37] However, assay methods used for determination of serum fT4 concentration including equilibrium dialysis (ED), considered as the gold standard assay, and the chemiluminescent enzyme immunoassay (CEIA) has been found to be of importance.[38] In Australia, fT4 determined by CEIA is more cost-effective, with a faster time to result compared to fT4 by ED. Currently, serum for fT4 by ED are sent to veterinary endocrinology laboratories in the USA via a courier service. Though good correlation exists between the assays, fT4 by CEIA consistently yielded lower results than measurements by ED (with a sensitivity 96% versus 98% respectively for diagnosis of hyperthyroidism), and CEIA did not identify more cats with hyperthyroidism compared to TT4 assays.[38] The overall higher sensitivity of fT4 compared to TT4 for diagnosing hyperthyroidism is compromised by a lower specificity of 93% compared to 100%.[37] Up to 12% of euthyroid cats may have elevated fT4 as a result of NTI, presumably as a result of decreased clearance of fT4,[39,40] contributing to the decreased specificity of fT4 compared TT4.[37,39,41] Overall, TT4 remains the first line assay for diagnosis of hyperthyroidism, as all cats with elevated TT4 will also have elevated fT4, and TT4 appears to have a sensitivity as good as fT4 by CEIA.[38]

For cases where serial measurements of TT4, followed by fT4 have returned within the RI, but clinical suspicion for hyperthyroidism remains strong, measurement of serum TSH could be considered. TSH is produced and secreted by pituitary thyrotrophs in response to thyrotropin-releasing hormone that is released from the hypothalamus when thyroxine and tri-iodothyronine concentrations fall. In hyperthyroid cats, TSH production and release are suppressed as thyroxine and tri-iodothyronine concentrations are high. Like fT4, TSH is a sensitive test for the diagnosis of hyperthyroidism; 98% of cats with confirmed hyperthyroidism have TSH concentrations below the detection limit of available assays, with only a few (2%) of cats with mild to moderate disease having detectable TSH.[42] Until recently, the only commercial assay validated to measure feline TSH (fTSH) has been a canine-specific chemiluminescent TSH (cTSH) immunoassay (IMMULITE®, Siemens Healthcare, Hawthorn East, VIC, Aust) due to significant cross-reactivity between fTSH and cTSH.[42] At the time of writing, this remains the only commercially available TSH assay for cats in Australia. Despite this cross reactivity, there are limitations in the assay specificity requiring the lower limit of quantification (LLOQ) to be set relatively high. As a result, some euthyroid cats and those with NTI who have mild to moderately decreased fTSH can may still have TSH concentrations below the LLOQ and are unable to be differentiated from hyperthyroid cats, compromising test specificity. Without a widely available feline specific TSH assay, TSH results are best interpreted in combination with T4 or fT4, to improve test specificity (from 70% to 99%) with little compromise on sensitivity.[42]

Zomedica (Ann Arbor, MI, USA), has recently validated a feline specific TSH assay, using bulk wave acoustic technology on their TRUFORMA® point-of-care diagnostic platform. Zomedica reports this fTSH assay as having a lower limited of quantification at 0.008 ng/mL, compared to 0.03 ng/mL with IMMULITE® which could potentially allow better differentiation of euthyroid from mildly hyperthyroid cats (White paper publication, Zomedica). However, external peer-reviewed validation of the assay remains outstanding and the assay's ability to differentiate hyperthyroid cats from clinically normal elderly cats or those with NTI require additional study. This technology is currently not available in Australia.

Dynamic thyroid function tests, such as the triiodothyronine (T3) suppression test thyrotropin-releasing hormone stimulation test or the TSH response test are rarely needed to diagnose feline hyperthyroidism. The T3 suppression test may be considered in select cases, if the diagnosis of hyperthyroidism cannot be achieved by measuring TT4, fT4 and TSH. Alternatively, a tertiary referral institution where thyroid scintigraphy is available could be recommended. This allows the assessment extent of radionuclide (typically technetium-99m) uptake by the thyroid gland in comparison to the salivary gland for the diagnosis of hyperthyroidism,[43,44] but also has the advantage for detection of functional extra-thyroidal foci and subjective differentiation between benign and malignant disease based on the pattern and distribution of uptake.[45,46]

Current treatment options for feline hyperthyroidism

Treatment of hyperthyroidism is aimed at limiting the excessive production of thyroid hormones. There are four main treatment modalities for feline hyperthyroidism: anti-thyroid medications, dietary iodine restriction, surgical removal of abnormal thyroid tissue or ablation of the hyper-functional thyroid tissue using radioiodine therapy.[1,47] The latter two modalities provide definitive treatment for the disease by permanent removal or destruction of abnormal thyroid tissue, while anti-thyroid medication and therapeutic diets require ongoing daily use to control thyroid hormone production.

Effective treatment restores normal metabolism and reverses the haemodynamic changes induced by hyperthyroidism, although cardiac structural remodelling occurs slowly, and while pre-treatment heart murmurs and echocardiographic abnormalities can resolve, new echocardiographic abnormalities can emerge in the months following treatment.[48]

Any GFR increases due to hyperthyroidism, are expected to reverse in treated patients with the establishment of euthyroidism. The GFR in treated hyperthyroid cats may stabilise below normal, unmasking previously subclinical CKD.[23] Reduced GFR can also be seen secondary to iatrogenic hypothyroidism, as discussed in further detail in the latter parts of this review. The advantages and disadvantages of the main treatment modalities are outlined in Table 1.

Anti-thyroid medications (thioureylenes)

The anti-thyroid drugs recommended for use in cats include methimazole and carbimazole. Methimazole is reported to be effective for treatment of feline hyperthyroidism in 95% of cases.[1] Methimazole can be administered either orally or as a topical gel, which is typically placed on the inner surface of the pinnae. Carbimazole is administered orally and is rapidly converted to an equimolar amount of methimazole after oral absorption. Due to differences in the molecular weights, 5 mg of carbimazole is equivalent to 3 mg of methimazole.[49] A dose of 2.5 mg methimazole (or 5 mg carbimazole) twice a day is recommended due to the best balance between efficacy and risk of adverse effects.[50] Dose and frequency are adjusted based on initial clinical severity and response to therapy. Thioureylenes inhibit the thyroid peroxidase enzyme, thus inhibiting the oxidation and organification of iodide, and ultimately the coupling of iodothyronines to form thyroxine and tri-iodothyronine.[51] Because anti-thyroid medications have no cytotoxic effects, the underlying adenomatous hyperplastic process continues over time and disease progression may lead to escape from long-term control. In a cohort of 2096 cats with hyperthyroidism treated with methimazole long term, disease severity, as defined by serum fT4 concentration and the thyroid-to-salivary gland ratio on scintigraphy, was observed to increase proportionally with disease duration.[5] Similarly, the prevalence of cats with SHIM-RAD or suspected thyroid carcinoma increased proportionally with disease duration; from 0.5% in the cohort of cats diagnosed with hyperthyroidism less than 12 months ago, to over 25% of cats with hyperthyroidism of more than 4 years duration. This trend suggests that transformation to malignancy is possible over time, although histopathology was not used to confirm thyroid carcinoma in these cases.[5] Regardless, this potential sequelae is an important consideration for hyperthyroid cats managed long term with medical therapy. Whilst extended survival has been reported in cats with SHIMA-RAD and thyroid carcinoma, recognition of this subgroup to allow for appropriate high dose radioiodine treatment is required, and owners should be prepared for frequent outcomes of hypothyroidism that will require ongoing management.[4,52]

Thioureylenes were previously recommended as the initial treatment of choice for all hyperthyroid cats, in ordero allow assessment of the effect of treatment of hyperthyroidism on renal function and therefore the suitability of the cat for definitive treatment. However, recent evidence suggests that this precaution may not be necessary. Although the unmasking of renal azotaemia can be unpredictable as GFR changes with establishment of euthyroidism, cats with a pre-treatment creatinine value of less than 177 µmol/L, equivalent to mid-stage 2 CKD according to the International Renal Interest Society (IRIS) guidelines,[53] are not expected to have shortened survival time should azotaemia develop due to unmasking of pre-existing renal disease by establishment of euthyroidism.[54,55]

Thioureylenes are recommended for the treatment of hyperthyroidism in moderately to severely azotaemic cats because dosage can be tailored to individual needs.[50] Treatment of hyperthyroidism appears essential regardless of CKD severity. Untreated hyperthyroid cats are vulnerable to ongoing kidney injury, as demonstrated by the common presence of proteinuria and elevation of markers of kidney function such as retinol binding protein.[56,57] These normalise with treatment of hyperthyroidism in cats without pre-existing CKD.[55–57] Treatment of hyperthyroidism in cats with moderate to severe CKD should be approached with caution due to the possibility of worsening renal function leading to exacerbation of uraemic signs with restoration of euthyroidism.[34,50] Thioureylene medications are ideal for treatment of hyperthyroidism in these cats as they are titratable to control hyperthyroidism as much as possible while avoiding clinical deterioration due to CKD.[50] Thioureylenes can also be used as a short-term solution for cats severely affected by hyperthyroidism to stabilise disease ahead of definitive treatment, if delays are necessary due to scheduling, or if general anaethesia is required.[58]

Iodine-restricted diets

Iodine is an essential component of thyroid hormones and limiting intake of dietary iodine leads to a reduction in thyroid hormone synthesis.[1] Dietary iodine restriction to less than 0.39 ppm on a dry matter basis has been shown to reduce circulating thyroid hormone to euthyroid concentrations in hyperthyroid cats.[59–62]

The commercial prescription diet Hill's Y/D is an iodine-restricted diet with an iodine concentration of 0.2 ppm on a dry matter basis.[61] This diet can normalise the TT4 concentration in 75%–83% of hyperthyroid cats within 2 months of exclusive feeding.[61] However, in contrast with other treatment modalities, target TT4 concentrations in the lower half of the RI are typically not achieved and clinical signs may not necessarily improve significantly.[61,63]

There is also ongoing debate regarding the nutritional composition of Hill's Y/D, which is marketed as appropriate for cats with concurrent CKD compared with maintenance diets, due to its moderate sodium, phosphorus and protein restriction. However, protein restriction can exacerbate protein malnutrition in hyperthyroid cats, where geriatric cats affected by hyperthyroidism are already expected to have a degree of sarcopenia.[64] Furthermore, the dry formulation contains the potential thyroid goitrogen of soy as the main filler ingredient,[65] and its relatively high carbohydrate content could exacerbate relative insulin resistance and glucose intolerance in the hyperthyroid state,[66,67] making Y/D diet a hesitant long term nutritional choice in hyperthyroid cats. With restoration of euthyroidism, it is expected that the catabolic state associated with hyperthyroidism resolves,[68] but significant reductions in creatinine concentration, reflective of an individual's muscle mass,[69] was documented despite the normalisation of TT4 in prospective studies on the effect of Hill's Y/D.[61,63,70]

Iodine-restricted diets need to be fed exclusively to achieve therapeutic effect.[61] The efficacy of dietary therapy may be reduced if owner or cat compliance is suboptimal. For individual cats, the palatability of the diet, may contribute to therapeutic failure. Thus, iodine-restricted diets may fail in approximately one-quarter of cats in the first months.[61] Dietary fluctuations in iodine may contribute to the development of hyperthyroidism,[20] and thus, switching between iodine-restricted and non-restricted diets due to poor palatability or poor compliance may be particularly counterproductive for treating hyperthyroidism.

In summary, dietary iodine restriction effectively lowers TT4 concentrations over time, but much is to be learned about the long-term

Table 1. Advantages and disadvantages of the current treatment modalities for hyperthyroidism

	Radioactive iodine	Thyroidectomy[73,75–78]	Thioureylenes[1,58,175]	Iodine restricted diet[60–62]
Potentially curative?	Yes	Yes	No; development of refractory disease and possible malignant transformation possible long term.	No; development of refractory disease and possible malignant transformation possible long term.
Need for ongoing therapy	No, though ongoing therapy might be needed if cat becomes hypothyroid.	No, though medical therapy for stabilisation prior to anaesthesia is ideal. Ongoing therapy might be needed if cat becomes hypothyroid.	Yes	Yes, and requires exclusive use of diet.
Need for anaesthesia	No, but potentially requires sedation.[176]	Yes	No	No
Hospitalisation	Country specific; typically 5–7 days in Australia.[176]	1–7 days	None	None
Treatment availability	Requires radiation safety expertise, licencing, and specialty facilities.	Requires surgical expertise.	Widely available.	Widely available.
Specific advantages	Treats all hyperfunctional tissue, regardless of anatomical location.	Excised tissue can be assessed histopathologically.	Titratable and reversible.	Titratable and reversible.
Owner factors	Separation during isolation.	Concern for anaesthesia/surgical risk.	Tableting may be difficult for owners, though transdermal formulations are available.	Owner and cat compliance may be a limiting factor. Requires exclusive feeding, difficult to achieve in cats with select appetite, and also for outdoor and multi-household cats.
Cost	High initial cost; some ongoing monitoring cost after treatment.	High initial cost; some ongoing monitoring cost after treatment.	Affordable short term, potentially costly long term.	Affordable short term, potentially costly long term. Less monitoring cost compared to thioureylenes.
Resolution of hyperthyroidism	95% based on literature of the last 20 years (Table 2) • 14% overt hypothyroidism • 4% persistent hyperthyroidism.	85%–90%, but long term outcome dependant on disease severity and surgical expertise. • 5–22% persistent or recurrence of hyperthyoridism.[73,75,77-79] • 28%–49% overt hypothyroidism[75,79]	95% responsive though potential to become refractory with time.	75%–83% response: Though target TT4 concentrations typically not achieved and clinical signs may not necessarily improve significantly.[61,63]
Potential adverse effects	• Rare, self-limiting acute GI signs such as dysphagia and vomiting • Hypothyroidism	• 6%–82% hypoparathyroidism • Hypothyroidism • Persistent hyperthyroidism if ectopic tissue present • Horner's syndrome • Laryngeal paralysis • Haemorrhage, or death intra-op	• 10%–25% self-limiting GI signs and lethargy • 3% facial pruritus and self-trauma • 3%–9% blood dyscrasias • Hepatic toxicosis • Rare immune mediated conditions such as myasthenia gravis[177,178]	Diet associated protein restriction could exacerbate protein malnutrition in hyperthyroid cats and geriatric cats; serum creatinine remains below RI despite resolution of TT4.[61,63,70]

effects of dietary iodine restriction in hyperthyroid cats. In the meantime, Hill's Y/D provides a treatment option for cats that are not candidates for definitive treatment and that cannot be treated with thioureylenes because of poor compliance or adverse effects.

Thyroidectomy

Thyroidectomy is an effective, definitive treatment modality for feline hyperthyroidism that does not require specialist equipment and can be performed in primary care hospitals.[1] Thyroidectomy is the only treatment modality that enables routine histopathological

evaluation of excised thyroid tissue. The general anaesthesia protocol for this procedure requires careful consideration for the management of the cardiovascular and haemodynamic changes associated with hyperthyroidism.[71] To minimise the metabolic and cardiac complications associated with hyperthyroidism, a period of stabilisation with medical therapy (anti-thyroid medications or iodine restricted diet) has been recommended in preparation for the procedure.[72]

The decision to perform a sub-total (unilateral) versus total (bilateral) thyroidectomy may not be straightforward. The prevalence of bilateral lobe involvement has been reported between 60% and 90% of hyperthyroid cats,[6,73,74] but lobe enlargement is often asymmetric.[6] Small, but hyper-functional lobes and ectopic thyroid tissue can be easily missed based on palpation alone.[45] Thus, thyroid scintigraphy is recommended before carrying out thyroidectomies to allow characterisation of the extent of thyroid disease.[45] If scintigraphy cannot be performed due to cost or availability, the post-operative risk of persistent or recurrent hyperthyroidism should be taken into consideration. Iatrogenic hypoparathyroidism and hypothyroidism also need to be considered. Reported rates of post-operative hypocalcaemia are highly variable, but apparently dependant on a combination of surgical experience and surgical approach. Extracapsular dissection technique for thyroidectomy has resulted in 82% (9/11) of cats with post-operative hypocalcaemia,[75] compared to 23% (6/26) of cat treated by the modified extracapular technique and 6% (5/86)–37% (7/19) of cats using a modified intracapsular dissection technique.[73,76] Report rates of hypocalcaemia based on unilateral versus bilateral thyroidectomies are not well defined, however, since a majority of cats with hyperthyroidism have bilateral involvement, the need for bilateral surgery is frequent.[73,74] Staging bilateral thyroidectomies (one side removed 3–4 weeks apart) has not been shown to significantly reduce the incidence of post-operative hypocalcaemia.[76] In affected cats, post-operative hypocalcaemia was reported to be mild and manageable with vitamin D and calcium supplementation. Post-operative prophylactic supplementation has not been shown to reduce the frequency of hypocalcaemia.[73,76]

Serum TT4 concentration is expected to decline to subnormal levels within 1–3 days of total thyroidectomy, but thyroid hormone supplementation is typically only considered in the initial weeks following surgery if there is concurrent rapid decline in renal function or if clinical signs of hypothyroidism are observed. These are often non-specific and mild such as weight gain and lethargy.[1] Long-term reports (beyond 4 weeks post-operatively) on the incidence of iatrogenic hypothyroidism following sub-total thyroidectomy are scarce. In one study, a serum TT4 concentration below the lower limit of the RI was seen in 13 of 46 (28%) cats beyond 6 months post-thyroidectomy; however, three of these cats had NTI. Other laboratory parameters such as TSH were not available for interpretation. A further 13 of 46 (28%) cats were already receiving thyroid hormone supplementation.[75]

Persistence or recurrence of hyperthyroidism in bilateral thyroidectomies performed at referral practices has been reported as between 5% and 11% at follow-up intervals of 3–59 months.[73,75,77,78] This finding was attributed to the presence of ectopic thyroid tissue that was not recognised or accessible during surgery,[73,77] or due to remnant adenomatous tissue left at the surgical site.[75] In a more recent retrospective study assessing thyroid changes after thyroidectomy in general practice, 15 of 68 (22%) cats had persistent or recurrent hyperthyroidism, while 33 of 68 (49%) cats were hypothyroid within 6 months of the surgery.[79] Where long-term follow-up data were available for 23 cats, 6 of 12 (50%) cats who were initially hypothyroid within 6 months of follow up had recurrence of hyperthyroidism. The remaining 6 (50%) cats had normalisation of TT4 at a median of 234 days after surgery. In total, 10 of 23 (43.5%) cats had recurrence of hyperthyroidism after bilateral thyroidectomy with a median follow up period of 726 days. The relatively large persistence or recurrence rate of hyperthyroidism, in addition to anaesthetic and surgical risks (such as iatrogenic hypoparathyroidism, Horner's syndrome and laryngeal dysfunction), are significant limitations to this treatment modality.

Radioiodine therapy

Functional hyperplastic or neoplastic thyroid follicular cells concentrate iodine, including radioiodine (radioisotope iodine-131). The beta particles emitted by radioiodine cause follicular cell death, and because they only travel 1–2 mm in tissue, neighbouring structures such as the parathyroid glands are minimally affected. Normal thyroid cells may also be spared because they are often atrophic in feline hyperthyroidism, secondary to physiologic negative hormonal feedback. Therefore, these thyroid cells fail to concentrate radioiodine. After ablation of the autonomous hypertrophic or neoplastic thyroid follicular cells, unscathed normal thyroid follicular cells are stimulated by TSH and resume function over time.[80] Effects of radioiodine treatment are rapid, with up to 90% of cats having TT4 concentrations within or below the RI by hospital discharge, which can be up to 3 weeks following treatment depending on local radiation safety laws.[81,82] Treatment failure as defined by persistent hyperthyroidism is uncommon, seen in an average of 4% of treated cats based on feline radioiodine treatment studies of the last 20 years.[83–89] The likelihood of treatment failure appears to increase with disease severity as defined by the TT4 concentration at either baseline (pre-treatment) or time of discharge post treatment. In a recent study of cats receiving radioiodine treatment, all 28 cats with TT4 concentration >150 nmol/L at discharge remained hyperthyroid long term, unless treated again.[82]

The earliest studies on radioiodine treatment used an intravenous route of administration.[90–93] Subsequent studies found that subcutaneous administration did not affect the treatment outcome compared with intravenous administration, and the subcutaneous route became the preferred parenteral route due to lower radiation exposure to personnel and avoidance of the added stress of venipuncture or intravenous catheterisation for the cat.[81,94,95] Oral administration have also been described, but historically administered at higher doses than what was recommended for parenteral administration due to the assumption of decreased bioavailability.[96,97] Formal pharmacokinetic and pharmacodynamic studies specific to radioiodine administration in cats have not been performed to test this assumption. Furthermore, veterinary studies directly comparing parentally versus orally administered radioiodine therapy with respect to doses used and outcome achieved are currently lacking.

Although oral administration of radioiodine is commonly used in humans, it has not been widely adopted in cats due the additional risk of vomiting following dosing, which may lead to treatment failure from inadequate dose absorption and increased personnel health and safety concerns due to higher radioactive spill risk. In Australia, at the time of writing, the injectable formulation of radioiodine is approximately twice the price compared with the oral capsule formulation when ordered as a single dose from the dispensing radionuclear pharmacy (Australian Nuclear Science and Technology Organisation, NSW, Aust). Rigorous licensing restrictions by the Australian Radiation Protection and Nuclear Safety Agency prevents preparation and distribution of radioactive material at referral hospital institutions.[98] Thus, oral administration has been adopted by Australian veterinary institutions (referral and general practice) offering radioiodine treatment, despite the shortcomings discussed. Interestingly, in a recent retrospective cohort study involving 161 cats given oral radioiodine at a standard dose (138 MBq) similar to the standard dose of 4 mCi (148mBq) described in the literature for parental administration, the rate of resolution of hyperthyroidism was comparable.[89,99] This finding contradicts the existing assumption that oral radioiodine should be given at a higher dose compared to parenteral radioiodine.

Radioiodine dose optimisation

Radioiodine dose optimisation for treatment of feline hyperthyroidism has been an ongoing point of discussion and research. Early studies employing radioiodine treatment for feline hyperthyroidism used a tracer dose of radioiodine and thyroid scintigraphy to calculate a dose aiming to deliver 15,000–20,000 rad/g of thyroid tissue based on the radioactive iodine uptake, effective half-life and weight of the thyroid gland in the cat.[90–92,95] A scoring system taking into account clinical severity, serum TT4 concentration and thyroid gland size based on palpation was later introduced to tailor the treatment while avoiding the additional cost and radiation exposure associated with thyroid scintigraphy. The score was designed to reflect the severity of hyperthyroidism as a guide for the most appropriate dose of radioiodine.[81,86,94,100,101] The use of a single fixed dose of radioiodine (ranging from 74–185 MBq) regardless of the degree of hyperthyroidism has also been evaluated. This method is logistically straightforward: there is no requirement for scintigraphy, and it results in a predictable decay in radioactivity to allow planning for the expected duration of isolation. Recently, a variation of these dose determination methods was suggested. This involved using thyroid scintigraphy to determine severity of disease and administration of a graded dose of radioiodine based on various scintigraphic criteria.[85] When treatment outcomes for cats receiving the graded dose were compared with those cats receiving fixed dose treatment, there was no significant difference between the groups. Similarly, there are comparable rates of resolution of hyperthyroidism for cats receiving a single fixed dose of radioiodine versus those given individualised doses.[87,93,96,97,102,103]

Table 2 outlines the outcomes of the various methods of radioiodine dose selection and administration reported in the literature. No studies have directly compared treatment outcomes for the different dose calculation methods and the variability in study samples, sample sizes, design and absence of standardisation of time to follow up make such comparisons difficult. The scoring system criteria, dose ranges and inclusion or exclusion criteria are also highly variable between studies, making it problematic to compare outcomes for the different dose calculation methods and for studies applying the same broad methodology. In addition, contrary to current times, iatrogenic hypothyroidism was once not recognised to be of clinical significance. Successful treatment of hyperthyroidism thus often included outcomes with TT4 concentrations both within and below the RI,[97] with no assessment of concurrent TSH or renal parameters, which may lead to under-estimation of 'hypothyroid' outcomes based on TT4 concentration below the lower limit of the RI alone. Nonetheless, as previously mentioned, all approaches have comparable results, with similar proportions of successful treatment, over-treatment and under-treatment.

With these findings, and because thyroid scintigraphy is not widely available, is costly and is associated with additional radiation exposure to cats and personnel, simpler dose calculation methods have become commonly used. An ideal scoring system should be applicable across cat populations and allow for a tailored dose that maximises successful treatment and minimises radiation exposure to personnel compared with a fixed dose regime, but this has not yet occurred. As a result, institutions offering radioiodine treatment have typically continued to use their established dose calculation and administration methods that have been guided by the availability of scintigraphy, cost and availability of radioiodine formulations and the regulations of local governing bodies.

As mentioned, single fixed oral radioiodine dosing has been adopted by most Australian institutions since the 1990s.[89,103–105] However, it remains to be determined whether this dose regimen remains appropriate for the current population of hyperthyroid cats. In recent times, the diagnosis of hyperthyroidism is occurring earlier in the disease process.[10,68] Although published doses administered parenterally have decreased for mildly hyperthyroid cats in recent years,[99] whether results from cats treated by the parenteral route can be extrapolated directly to cats treated orally is unknown. Information regarding intermediate or long-term follow-up of cats treated with a fixed oral dose of are limited, and no studies focused on iatrogenic hypothyroidism and the impact on renal parameters in these cats. Therefore, it is currently not known whether the standard 138 MBq fixed oral dose used in Australia remains appropriate, though more than likely, use of lower doses will be explored in the coming years given concerns regarding over treatment increasing the risk of hypothyroidism and thus pathologically lowering GFR.

Hypothyroidism after radioiodine treatment

Hyperthyroidism causes suppression of pituitary TSH secretion.[106] Recovery of pituitary thyrotrophs following radioiodine therapy and re-establishment of normal feedback mechanisms is expected to take up to 3 months, preventing early differentiation between transient and permanent iatrogenic hypothyroidism.[107]

Overt hypothyroidism is defined as a TT4 concentration below the RI with a concurrent TSH concentration above the RI, and subclinical hypothyroidism is defined as a TT4 concentration within the RI (usually toward the lower end) with a concurrent TSH concentration

Table 2. Existing studies assessing the outcome of radioiodine treatment in hyperthyroid cats grouped by method of dose determination

	Study	N	Dose in MBqMedian/ mean (range)	Route	Post treatment outcome (%)				Follow-up period post-treatment (months)
					Euthyroid	Subclinically hypothyroid	Overt hypothyroidsm	Persistent hyperthyroidism	
Calculated dose	Turrel et al.[90]	11	(37–218)	IV	64		18	18	2–18
	Meric et al.[91]	29	(56–227)	IV	83		7	10	1
	Theon et al.[95]	60	134 (SD 78–190)	IV	85		7	8	1–48
		60	134 (SD 93–175)	SC	84		5	11	1–48
Scoring system	Jones et al.[100]	32	(39–100)	IV	88		3	9	3–4
	Malik et al.[97]	40	(200–300)	PO	90			10	<1
	Mooney[94]	50	143 (80–200)	SC and IV	80		14	6	3–32
	Slater et al.[179]	236	181 (104–329)	IV	85		9	4	13–18
	Peterson et al.[81]	524	111 (74–222)	SC	87		11	2	3–12
	Feeney et al.[84]	97	(113–224)	PO	65		32	3	2–3
	Peterson et al.[83]	131	69 (37–74)	SC	95		3	2	1–3
	Morré et al.[85]	57	111–167	SC	54	12	18	16	6
	Peterson et al.[109]	262	70 (44–514)	SC	80	18	2	0	4–8
	Fernandez et al.[86]	55	130 (74–222)	SC	40	13	40	7	6–9
	Buresova et al.[164]	47	143 (68–455)	IV	88	6	4	2	1
	DeMonaco et al.[172]	84	96 (48–167)	SC	68	19	13	0	3–6
	Peterson and Rishniw[101]	1380	70 (37–392)	SC	75	17	4	4	12
Fixed dose	Klausner et al.[96]	22	185	PO	82		9	9	3–38
	Meric et al.[102]	60	148	IV	88		3	8	2–28
	Craig et al.[93]	65	150	IV	88		8	4	2–33
	Dietze el al.[103]	67	154	PO	45		52	3	1
	Chun et al.[87]	193	148	IV	90		9	1	1–12
	Lucy et al.[99]	39	148	SC	36	46	18	0	6
	Lucy et al.[99]	150	74	SC	75	21	1	3	6
	Morré et al.[85]	23	167	SC	48	17	26	9	6
	Finch et al.[88]	20	111	SC	70	5	15	10	12
	Yu et al.[89]	161	138	PO	83		15	2	6

Where studies have two or three columns combined, results did not give the percentage breakdowns differentiating these.
IV, intravenous; PO, oral; SC, subcutaneous.

above the RI.[108] These definitions do not consider or refer to the presence of clinical signs. Clinical signs attributable to hypothyroidism, such as lethargy, weight gain and poor appetite, are inconsistently observed in iatrogenically hypothyroid cats. When present, they can be mild and similar to signs related to successful resolution of the hyperthyroid state.[108] Iatrogenic (subclinical or overt) hypothyroidism can be documented in 15% of the population at 1 month and up to 80% at up to 6–9 months post radioiodine treatment.[80,86,88] Although approximatrely one third of iatrogenically hypothyroid cats have been shown to recover normal thyroid function within a few months, additional cats may develop subclinical or overt hypothyroidism over as long as 12–18 months post-treatment, indicating the necessity for extended follow-up for radioiodine treated cats.[80,88,107]

The consequence of iatrogenic hypothyroidism on renal function is of clinical importance. Williams et al. performed a retrospective cross-sectional study assessing the relationship between thyroid status and the presence of azotaemia in hyperthyroid cats.[107] The cats were treated with anti-thyroid medication alone or in combination with thyroidectomy and the outcomes were assessed at least 6 months after commencing treatment. Williams et al. found a significantly higher proportion of cats with azotaemia in the overtly hypothyroid group (16 of 28 [57%]) compared with the euthyroid group

(14 of 47 [30%]). In addition, cats that developed azotaemia in the face of overt hypothyroidism at and beyond 6 months post-treatment had a shorter survival time (median 456 days) compared with non-azotaemic cats (median 905 days).[107] When TT4, TSH and renal biochemistry markers were assessed up to 18 months after low-dose radioiodine therapy, the prevalence of new or worsening azotaemia was consistently higher in hypothyroid (overt and subclinical) cats than in euthyroid cats.[80,88,89,109] In addition, the prevalence of azotaemia in cats with overt hypothyroidism has been shown to be higher compared to cats with subclinical hypothyroidism.[86,109]

The long term clinical significance of subclinical iatrogenic hypothyroidism in cats requires further examination, however, a similarly cautious approach as with overt hypothyroid cats with regards to surveillance of renal function would be sensible. In humans, an increased prevalence of CKD have been documented in those with subclinical hypothyroidism.[110] Furthermore, humans with subclinical hypothyroidism were less likely to develop end-stage CKD if they received levothyroxine supplementation compared to a placebo.[111]

A TT4 concentration that is below the RI should prompt the clinician to consider either the development of iatrogenic hypothyroidism or the presence of concomitant NTI in cats that were previously treated with radioiodine. Diseases known to consistently suppress TT4 include renal disease, systemic neoplasia, gastrointestinal disease, hepatopathies and endocrinopathies, although degree of TT4 suppression correlates more with the degree of systemic illness than the specific disease type.[112]

Further investigation to differentiate between iatrogenic hypothyroidism and NTI can include measurement of fT4 or TSH and thyroid scintigraphy.[106] Thyroid scintigraphy highlights functional thyroid tissue through thyroidal uptake of radionuclides. Quantitative scintigraphy has been used to diagnose spontaneous hypothyroidism in dogs,[113,114] and is commonly used to assess post-radioiodine treatment efficacy in humans.[115,116] This is considered to be the gold standard diagnostic imaging modality for thyroid dysfunction in dogs, cats and humans but has not been validated as a test for iatrogenic hypothyroidism in cats.[38,45,117] A potential limitation of scintigraphy for assessing post-radioiodine treatment thyroidal function is the dependence of circulating TSH for iodide (and presumably also technetium) uptake in non-adenomatous thyroid tissue.[118] This relationship is yet to be formally assessed in radioiodine treated cats, but since TSH may still be down regulated in the early (3 months) post-treatment period,[107] reduced technetium uptake should be interpreted in light of concurrent TSH concentrations. Practically, the cost and facility requirement for scintigraphy typically prohibits its routine use in the assessment of feline thyroid function post-radioiodine treatment, thus clinicians largely rely on endocrine assays for this purpose.

Although fT4 is less influenced by NTI than TT4,[39] and can even be elevated with NTI, it may also decrease below the RI with increasing severity of NTI.[37,112] The sensitivity and specificity of fT4 or diagnosing iatrogenic hypothyroidism has not been explicably established. Furthermore, studies performed so far suggests there is no advantage in using fT4 over TT4 in the diagnosis of radioiodine induced hypothyroidism. Normal TT4 and fT4 were documented in 13 of 28 (46%) and 21 of 28 (75%) scintigraphically diagnosed hypothyroid cats (supported by concomitantly elevated cTSH) respectively.[117]

TSH is considered to be both a sensitive and specific for diagnosing spontaneous or iatrogenic hypothyroidism.[117,119] An elevated TSH has been shown to be more sensitive than a below RI value for both TT4 and fT4 for the diagnosis of iatrogenic hypothyroidism. TSH was also able to differentiate cats with iatrogenic hypothyroidism from euthyroid cats with CKD (NTI), supporting assay specificity in this context.[117] Based on feline radioiodine studies emerging from the last 5 years, it is now becoming the standard to differentiate between euthyroid and subclinical hypothyroid outcomes (Table 2), making TSH an increasingly important assay as a part of post radioiodine treatment monitoring. A recent study comparing outcome of a low dose (73 MBq subcutaneous injection) versus the classical dose (148 MBq subcutaneous injection) of radioiodine found no significant difference in the rate of persistent hyperthyroidism between the two groups. However, subclinical hypothyroidism was more common at 6 months post-treatment following classical dose administration.[99]

In another study evaluating outcomes using TT4 and TSH concentrations following low-dose (median 78 MBq subcutaneous injection) of radioiodine, iatrogenic hypothyroidism (both subclinical and overt) was documented in 85 of 569 (15%) cats at 1 month post-treatment, with 23 (27%) of these 85 cats being overtly hypothyroid.[80] Ultimately, when followed for more than 18 months, 23% of the population became hypothyroid, although only 5% of these cats were overtly hypothyroid and few had clinical signs attributable to hypothyroidism. In this study, transient hypothyroidism was seen in 30% of untreated hypothyroid cats and the median time to normalisation of both TT4 and TSH was 6 months, but in 25% of these cats, transient hypothyroidism took 12 months or more to resolve. Whether subclinical hypothyroidism progresses to overt hypothyroidism in cats treated with radioiodine remains to be determined. In humans, 2%–6% of patients with subclinical hypothyroidism will progress to overt hypothyroidism with each year following radioiodine treatment.[120–122]

Recognition that the development of iatrogenic hypothyroidism after treatment of hyperthyroid cats is detrimental to renal function and may negatively affect long-term survival has further highlighted the importance of dose optimisation in radioiodine therapy.[80,107]

Feline hyperthyroidism and kidney function

The classical markers of renal function, serum creatinine and serum urea nitrogen, are indirect markers of GFR. These markers are considered insensitive at detecting renal dysfunction because there needs to be approximately 75% loss in functional renal mass before creatinine increases above the RI.[123] In addition, extra-renal factors such as signalment, muscle mass and daily variability in exogenous and endogenous protein loading can result in an inaccurate assessment of renal disease status.[33,124] As previously discussed, hyperthyroidism artificially increases renal blood flow and GFR. Metabolic disturbances such as increased endogenous protein catabolism and muscle wasting from the hyperthyroid state further obscure the ability to accurately assess kidney function with creatinine and urea concentrations.[9,33] Successful treatment of hyperthyroidism reduces GFR,

allowing for a more accurate correlation between creatinine, urea and renal function and better identification of cats with CKD.[125–127]

Despite the artificial increase in GFR of hyperthyroid cats, 10%–23% of cats are reported to have concurrent azotaemia at the time of diagnosis of hyperthyroidism.[9,107,128] This is higher compared to the prevalence of CKD in the general population, which is estimated at 1.2% (95% CI 1.1 to 1.3%), increased to 3.6% (95% CI 3.3 to 3.8%) in cats aged ≥9 years of age.[129] Thus hyperthyroidism is a well reported risk factor for CKD diagnosis,[55,57] with the odds ratio for hyperthyroid cats with a concurrent diagnosis of CKD being 5.7 (95% CI 2.8 to 11.7, $P < 0.001$).[129] Following treatment of hyperthyroidism with methimazole or radioiodine, the prevalence of azotaemia has been reported to be 17%–49%.[125,128,130,131] TSH was not measured in these studies, and thus it is not possible to determine whether iatrogenic hypothyroidism (leading to subnormal renal blood flow and GFR) or the unmasking of pre-existing CKD (with restoration of normal renal blood flow) had led to occurrence of azotaemia. In studies where TSH was assessed concurrently, 57%–66% of cats with abnormal kidney function following radioiodine treatment (as determined by creatinine or GFR) were found to have iatrogenic (subclinical or overt) hypothyroidism[86,88,117] as compared to 11%–20% of cats with euthyroid outcomes.[86,88,109]

Although the diagnosis of concurrent overtly azotaemic renal disease in hyperthyroid cats is associated with shorter survival times following radioiodine treatment,[128] for cats that are not azotaemic at the time of treatment, the unmasking of azotaemia subsequent to effective treatment for hyperthyroidism does not affect survival.[54,55] Regardless, a predictive marker for post-treatment azotaemia has long been sought since it would allow clinicians to manage owner expectations regarding the development of CKD following radioiodine treatment and for appropriate planning to take place, including closer monitoring and instigation of reno-protective medical interventions aiming to slow the progression of CKD. Weighing and managing the risk of iatrogenic hypothyroidism becomes particularly important in these cats.

To date, a sensitive and specific predictive marker of pre-existing CKD in hyperthyroid cats remains elusive. Table 3 summarises the studies that have been performed to investigate whether specific pre-treatment clinical parameters can predict unmasking of CKD after radioiodine therapy prior to the commercial availability of SDMA.

The pre-treatment GFR potentially has predictive value in the development of post-treatment azotaemia,[125,132,133] yet previously established cut-offs[127] may be insensitive.[126] Sensitive and specific cut-offs may be difficult to establish, possibly because pre- and post-treatment GFR are both influenced by factors other than the cats' thyroid status.[125,132] An added consideration is the practicality of GFR measurement in clinical practice. This test requires injection of a filtration marker, such as exogenous creatinine, inulin or preferably, iohexol, followed by acquisition of single or multiple blood samples at specific time intervals to evaluate renal clearance.[134] The process is straightforward provided there is access to a laboratory offering the assay for iohexol. Formulae for determining GFR using limited sampling plasma clearance methods in cats have been published, so potentially the clinician does not have to rely on the laboratory to provide the calculated GFR.[134] However, access to a commercial reference laboratory that offers the iohexol assay remains the limiting factor of GFR determination in Australia. Currently, there are no Australian veterinary laboratories that provide this service, thus plasma iohexol measurements require an established relationship with a research or human clinical pathology laboratory, or shipping to overseas locations for analysis, which adds cost and causes significant delays in the diagnostic process. GFR can also be measured using nuclear scintigraphy,[135] but limited access to facilities, sedation requirement and expense precludes its routine use. In addition, the RIs change depending on the methodology used to determine GFR, making application of derived reference values difficult to extrapolate to all clinical scenarios.

SDMA as a marker of renal function

Symmetric dimethylarginine, a relatively new serum biomarker, has been shown to have good correlation with GFR and is generally considered to be more sensitive than creatinine for detecting renal dysfunction in cats.[136,137] Both SDMA and its structural isomer, asymmetric dimethylarginine, are post-translational methylated arginine residues that are released into circulation as a by-product of intracellular protein catabolism.[138,139] Studies in people have shown that the relationship to renal excretory function is much stronger for plasma SDMA than for asymmetric dimethylarginine. Because asymmetric dimethylarginine is highly protein bound, it is largely cleared by enzymatic hydrolysis and urinary excretion accounts for less than 20% of the asymmetric dimethylarginine metabolism.[139] Meanwhile, due to SDMA's small molecular size and positive charge, it is freely filtered at the glomerulus. More than 90% of SDMA are excreted by the kidneys, thus plasma concentrations are affected by changes to GFR, and therefore renal blood flow.[139,140]

As one of the earlier veterinary studies investigating the role of SDMA as a surrogate marker of renal function, Hall et al. followed healthy geriatric cats ($N = 21$) and cats with CKD ($N = 21$) to show both SDMA ($r = -0.79$; $P < 0.0001$) and creatinine ($r = -0.77$; $P < 0.0001$) as having similarly moderate, but significant correlation with GFR. There was also a moderate, but significant relationship between SDMA and creatinine ($r = 0.72$; $P < 0.0001$), but serum SDMA concentrations were more sensitive (100% vs 17%) though less specific (91% vs 100%) than creatinine in detecting a GFR reduction of more than a 30% decrease below the median GFR of healthy cats (<1.36 ml/min/kg).[137] In this study, an SDMA concentration of 14 µg/dL corresponded to a 24% decrease from the median GFR of healthy controls. Furthermore, SDMA increased to above the RI on average 14.6 months earlier than creatinine.[137]

In more recent studies, both SDMA and creatinine correlated moderately to GFR,[141] but less strongly compared to previous studies, and showed similar sensitivity and specificity in the detection of decreased GFR.[137] Although these studies are not directly comparable as a result of different study populations, methodologies in measuring GFR, laboratory quantification techniques of SDMA and creatinine, they do cast doubt on the previously established superiority of SDMA over creatinine as a surrogate marker for GFR.[142,143] Future studies that directly correlate SDMA, creatinine and GFR in larger cat populations, particularly those with pre-clinical renal disease and

Table 3. A summary of studies assessing potential predictive markers for subclinical kidney disease in hyperthyroid cats prior to the commercial availability of symmetric dimethylarginine

References	Sample size	Potential predictive pre-treatment variable measured	Conclusion relating to development of post-treatment azotaemia
Adams et al.[127]	22	Serum TT4, creatinine, urea, USG and GFR (measured by nuclear scintigraphy)	A pre-treatment GFR of 2.25 ml/kg/min had 100% sensitivity and 78% specificity for predicting presence of CKD 30 days post-treatment. Pre-treatment urea, creatinine and USG were not significantly different between azotaemic and non-azotaemic cats 30 days post-treatment.
Syme et al.[180]	25	UPC	Pre-treatment UPC did not differ between cats that developed CKD and cats that did not at 6 months post-treatment.
Riensche et al.[131]	39	Serum TT4, creatinine, urea, phosphorus, potassium, UPC, USG	No significant difference in any pre-treatment parameters measured between cats that developed CKD versus cats that did not 6 months post-treatment.
Boag et al.[125]	24	Serum TT4, creatinine, urea, total protein, albumin, alanine aminotransferase, alkaline phosphatase, glucose and GFR (measured by serum inulin clearance)	A significant difference in pre-treatment GFR was found between cats that had a GFR below the RI and cats that did not 6 months post-treatment. However, there was an overlap between the two groups and a pre-treatment GFR cut off could not be determined. Pre-treatment glucose was associated with decreased GFR post-treatment, but the significance of this finding was not established.
Van Hoek et al.[132]	21	Serum TT4, GFR (measured by plasma iohexol clearance), UPC and urine retinol binding protein	A significant difference was found between pre-treatment GFR, USG and TT4 concentrations between cats that had post-treatment CKD of < IRIS stage 2 CKD and cats that had ≥ IRIS stage 2 CKD 4 weeks post-treatment. Further research is necessary to develop pre-treatment cut off values for this to be clinically applicable.
Kongtasai et al.[181]	45	Serum TT4, TSH, creatinine, GFR, L-FABP, NGAL, urine L-FABP and NGAL	No difference in serum L-FABP, NGAL and urine NGAL in hyperthyroid compared to healthy cats. Serum L-FABP did not change between pre and post radioiodine treatment timelines. Urine L-FABP was increased in hyperthyroid compared to health cats and these values normalised after euthyroidism was restored. Low number of post treatment azotaemia prevents assessment of uL-FABP to predict post treatment azotaemia.

CKD, chronic kidney disease; GFR, glomerular filtration rate; L-FABP, liver fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin; TT4, total thyroxine; TSH, thyroid stimulating hormone; UPC, urine protein creatinine ratio; USG, urine specific gravity.

extra-renal comorbidities that lead to increased protein catabolism or altered SDMA metabolism are warranted.

The established upper reference limit of SDMA for the cat is 14 µg/dL, based on data derived from measuring SDMA by liquid chromatography–mass spectrometry in 86 apparently healthy adult cats aged 6–15 years and weighing 3–9 kg (Unpublished data from IDEXX Laboratories Inc, Westbrook, ME, USA). This reference limit was established without comparison to classical measures of renal function such as GFR or creatinine.

Early veterinary studies measured SDMA using liquid chromatography–mass spectrometry.[136,137,144,145] While this is the gold standard for SDMA, its utility is limited to high-volume clinical laboratories. IDEXX laboratories has since developed a high-throughput competitive homogenous immunoassay, followed by a point of care Catalyst® SDMA test utilising their Catalyst Dx® Chemistry Analyzer. Both have comparable performance to liquid chromatography–mass spectrometry based on a combination of unpublished studies and white paper publications from IDEXX Laboratories Inc, Westbrook, Maine, USA.[146]

SDMA has been recognised and incorporated as an adjunctive parameter in the IRIS guidelines for diagnosis, staging, monitoring and therapeutic planning of CKD.[53,142] This addition aimed to improve the accuracy of IRIS staging where creatinine is affected by

extra renal factors such as increased endogenous protein catabolism and muscle wasting. Furthermore, given the presumptive high sensitivity of SDMA in the context of detecting early renal dysfunction,[137,142] even in animals with normal muscle condition, a repeatable SDMA concentration of >18 µg/dL in the face of concurrent normal creatinine concentrations (IRIS CKD stage 1 based on creatinine) can be used to assign IRIS stage 2 CKD status.[53] This recommendation by IRIS was supported by a recent longitudinal study showing 24%–92% of cats with persistent SDMA elevations (with concurrent normal creatinine concentration) will develop concordantly increased creatinine concentrations over the next 2 years, with the probability of concordant results increasing as the baseline SDMA concentration increases, supporting the concern of persistent or progressive decline in renal function in animals with persistently elevated SDMA.[147] Furthermore, a recent study assessing the GFR, SDMA and creatinine concentration of non-azotaemic dogs found a SDMA cut-off of >18 µg/dL optimised both sensitivity and specificity of a decreased GFR.[148] A parallel study in cats not yet available. By accurately staging CKD patients, the management and prognosis of these patients can be optimised by allowing for earlier clinical intervention, discontinuation of nephrotoxic medications and proactive monitoring.[149]

Extra-renal factors affecting SDMA

In a cross-sectional analysis of healthy geriatric cats, SDMA had a weak positive correlation with age ($r = 0.38$, $P = 0.03$), which likely reflects the relationship of decreasing GFR with increasing age ($r = -0.31$; $P = 0.01$). This study found no significant effect by the total lean mass or sex on SDMA.[124] Birman cats have a normal physiological concentration of creatinine and urea that is higher than the general feline population.[150] In a study assessing SDMA concentration in 50 healthy Birmans, both SDMA and creatinine were significantly higher in Birmans compared with non-Birmans; however, SDMA was elevated above the reference limit less frequently compared with creatinine.[151] Although a Birman breed-specific RI for SDMA was formulated based on this study's sample, there was significant overlap with the existing RI and wide confidence intervals associated with the upper limit of normal. Thus, the study concluded that SDMA was a better marker of renal function than creatinine in Birman cats, although the existing reference limit for SDMA was still appropriate and that analysis of both SDMA and creatinine was most ideal in the staging of renal disease in Birman cats.

The RI established by IDEXX Laboratories in adult cats also applies to kittens aged 1–12 months. Although, sedated kittens less than 6 months of age had significantly higher SDMA concentrations compared with un-sedated kittens. The degree of SDMA elevation was most dramatic in the youngest kittens aged 1–3 months. The authors postulated that the increase in SDMA in this scenario is from decreased renal blood flow leading to decreased GFR as a result of sedation-related vasoconstriction.

There is currently limited literature available regarding non-renal related disease states of cats and their effects on SDMA. In 40 cats with hypertrophic cardiomyopathy, the serum SDMA concentration was not significantly different from healthy control cats.[152] However, in the same study, 17 cats with diabetes mellitus were found to have significantly lower SDMA concentrations compared with healthy controls. The reason for this requires further research, but increased cellular uptake, hepatic metabolism and renal hyperfiltration associated with diabetes mellitus have been proposed as pathophysiological explanations in people with type 2 diabetes.[153,154] In a different study of similar sample size, no significant difference was found in GFR, creatinine and SDMA concentrations of cats with poorly controlled diabetes mellitus and healthy cats.[141]

In dogs, no correlation was found between SDMA and the myxomatous mitral valve disease, congestive heart failure and its pharmacological treatment for subsequent congestive heart failure.[155] However, a relationship between SDMA and cancer is suspected and warrants further exploration. A preliminary study in 10 dogs and 9 cats with various neoplasms found mild to moderate SDMA elevations from 8 to 26 µg/dL in 7 patients, though this was explained by presence of CKD or neoplastic infiltration on renal histopathology post mortem.[156] Interestingly, in the retrospective component of this study, 15% of 50 dogs and cats with neoplastic disease had increased SDMA, compared to only 2% with creatinine elevations.

Canine lymphoma has since been singled out as a neoplastic disease where SDMA elevations appear common; 11 of 14 dogs with various lymphoma were found to have elevated SDMA concentrations without concurrent azotaemia. Only one of these dogs had renal lymphoma, and none had pre-existing CKD. With clinical remission following chemotherapy, SDMA was normalised in all dogs.[157] In these cases, mechanisms other than alterations in GFR (caused by tumour infiltration) may be responsible for SDMA elevation in these patients. Considerations include alterations in protein turnover in malignancies to increase productions of dimethylarginines, or alterations in the selectivity of glomerular basement membrane from neoplastic cells preventing the filtration of cationic SDMA molecules, while non-polar creatinine is filtrated as normal. Further work is required to ascertain the pathophysiological mechanism of increased SDMA in lymphoma, and whether SDMA can be used as a biomarker of disease and response to treatment in these patients. Whether these associations are repeatable in feline lymphoma remains to be established.

Although it has been proposed that SDMA plays a role in the variability of nitrite and nitrate production, and thus vascular endothelial function,[158] no association was found between plasma SDMA and systolic blood pressure in a study evaluating SDMA among other markers in normotensive and hypertensive cats with variable azotaemia.[145]

An important additional consideration for interpretation of the SDMA assay is the potential for normal fluctuation of SDMA concentration within a patient. The index of individuality (IOI) describes the relationship (ratio) between intra- and inter-individual variability for a diagnostic test.[159] In both dogs and cats, the IOI is intermediate for SDMA, suggesting that while a population based RI may be appropriate, a value may also fall within the reference limit but outside an individual's homeostatic set point.[160,161] The detection of abnormality in an individual may require assessment through sequential SDMA measurements to demonstrate a minimum change exceeding the total biologic variability that establishes the limits of

normality of the assay. The reference change values in cats for serum SDMA is established as 53%–61% depending on the assay used. This means a clinician can attribute a clinically relevant change in SDMA concentration between two sequential measurements with values >53% above or below the previously determined concentration.[161,162]

SDMA and feline hyperthyroidism

Creatinine results above the RI were seen in only 3.5% of hyperthyroid cats (N = 2000) compared with 14% of the general feline population older than 5 years of age (N = 453,126). In contrast, the SDMA concentration was above the RI in 20.6% of hyperthyroid cats compared with 27% of the general feline population. (Unpublished data from IDEXX Laboratories, Inc, Westbrook, ME, USA.) The disparity between creatinine and SDMA in the hyperthyroid population may be due the dependency of creatinine on the muscle mass of an individual,[69] which can be significantly decreased in the catabolic state of hyperthyroidism.[68] SDMA is not affected by muscle mass, thus it could be insinuated that SDMA may be a better diagnostic test for detecting masked CKD in hyperthyroid cats before treatment. However, SDMA is a by-product of intracellular catabolism and is almost exclusively excreted by the kidneys. As a result, SDMA is influenced by both renal blood flow and basal catabolism. Since both factors are affected by the thyroid hormone, how thyroid dysfunction and its subsequent correction influences the clinical interpretation of SDMA has been researched repeatedly, but without consensus.

When laboratory data were used to assess the change in SDMA, creatinine, TT4 and body weight before and after treatment of 1281 hyperthyroid cats by any modality, creatinine continued to increase at all time points from baseline as the cats gained weight, up to 120 days post treatment.[163] SDMA increased from 1 to 30 days post treatment, but plateaued beyond this point. Evidence contradicting this finding comes from a smaller study of 47 cats that found that SDMA did not significantly change during the first month following treatment, while creatinine did increase significantly.[164]

Several other small-scale studies have examined the relationship between SDMA, TT4, creatinine and GFR. These studies have suggested that SDMA concentration may not always differ between healthy and hyperthyroid cats.[165,166] Furthermore, there are no consistent correlations between SDMA, GFR and TT4 across studies,[164,167] though it is likely that these studies were statistically underpowered.

An understanding of the influence of hyperthyroidism on the metabolism of SDMA in cats and dogs is still developing. In people with thyroid disease, L-arginine derivatives are increased in both hyperthyroidism[168,169] and hypothyroidism compared with controls.[170] In dogs with naturally occurring hypothyroidism, creatinine was above the RI of 124 µmol/L in 30% of dogs, compared to 50% of dogs with elevated SDMA above the RI of 14 µg/dL. In the majority of these dogs, creatinine (7 of 8 dogs) and SDMA (10 of 12 dogs) normalised following levothyroxine supplementation.[171] As GFR was not concurrently measured in these dogs, it was not possible to tease out potential renal and pre-renal causes for these outcomes.

Peterson et al. found the pre-radioiodine treatment SDMA concentration of a group of hyperthyroid cats (N = 262) to have poor sensitivity (33.3%), but high specificity (97.7%) for detecting masked renal azotaemia.[109] Creatinine, at the established cut-off concentration of 168 µmol/L, was also poorly sensitive (11.9%), but highly specific (100%). Peterson et al. also found a weak, positive relationship between SDMA and creatinine at baseline ($r = 0.325$, $P < 0.001$) and a very weak ($r = -0.12$; $P = 0.05$) relationship between and SDMA and TT4. At a median post-treatment follow-up interval of 6 months, these relationships were moderate ($r = 0.664$, $P < 0.001$) and weak ($r = -0.22$; $P < 0.001$) respectively. These relationships were repeatable in a more recent, but smaller study,[172] where findings suggested SDMA concentrations in the un-treated hyperthyroid cats were mainly influenced by GFR, and effects of the hypermetabolic state on SDMA were likely negligible.

Data contradicting the specificity of SDMA in detecting masked renal dysfunction were presented by Buresova et al.[164] where the GFR was measured in 10 hyperthyroid cats; no significant relationship between SDMA and GFR was found before ($\tau b = -0.3$; $P = 0.17$) and 1 month after ($\tau b = -0.22$; $P = 0.41$) radioiodine treatment, whereas the relationship between creatinine and GFR was moderate and significant at both time points; ($\tau b = -0.52$; $P < 0.05$) and ($\tau b = -0.53$; $P = <0.05$) respectively. Furthermore, this study only found a weak correlation between SDMA and creatinine before and 1 month after radioiodine treatment. Limitations of this study include the limited follow up period and a GFR study sample size of only 10 cats.[164]

In another prospective study assessing the relationship between SDMA and creatinine, the correlation was poor ($r = 0.13$; $P = 0.25$) and moderate ($r = 0.53$; $P < 0.001$) at baseline and 3 months after oral radioiodine treatment respectively,[173] similar to Peterson et al. However, serum SDMA failed to increase in 28% (21 of 75) cats following radioiodine treatment, including 5 cats that had TT4 concentrations below the lower limit of the RI. This was unexpected, as cats with presumptive iatrogenic or overt hypothyroidism (TSH was not concurrently measured) would be expected to have a declining GFR.[88,174] Serum creatinine behaved more predictably in this study, increasing in all but two cats following radioiodine treatment, hence there was little surprise to find poor agreement between SDMA and creatinine when used for IRIS CKD staging in cats following radioiodine treatment.[173] Such discordant outcomes between SDMA and creatinine support the suggestion that extra-renal factors interfere with the specificity of SDMA in hyperthyroid cats before and after radioiodine treatment.

Based on the limited studies currently available, it appears that thyroid status, renal function and SDMA have a complex interplay. Though initial studies have suggested excellent specificity of SDMA for identifying renal dysfunction in hyperthyroid cats, subsequent studies have shown SDMA concentrations to change inconsistently after radioiodine treatment. Furthermore, a significant and consistent correlation between SDMA and GFR in these cats has not been demonstrable, though larger studies assessing this are lacking. Additional studies are required to understand the potential extra-renal interference in the use of SDMA in hyperthyroid cats, indicating that SDMA cannot be used in insolation in this population of cats and

the desirable predictive marker of pre-existing CKD in hyperthyroid cats remains elusive.

Conclusion

Feline hyperthyroidism is the most common endocrinopathy affecting middle-aged to geriatric cats, and comorbid CKD occurs commonly in hyperthyroid cats. Although feline hyperthyroidism is a potentially curable disease, most commonly achieved with radioiodine, further work is required to establish the ideal dosing parameters for this treatment. It is likely that comparatively lower doses will be adopted with time, possibly reflecting increasingly milder disease presentations, in the attempt to minimise overtreatment and the associated negative effects on renal function and survival.

The importance of extended monitoring post radioiodine treatment of both thyroid and renal function for up to and beyond 12 months from treatment have become apparent in recent years. Thyroid status can continue to change beyond the typically 3–6 months that treated cats have historically been monitored for. In addition, subclinical hypothyroidism has become a treatment outcome of interest and importance in recent years, adding a new layer of nuance to post radioiodine treatment monitoring.

Assessment of thyroid status may need to include both TT4 and TSH assays in cats that become azotaemic following radioiodine treatment to determine if this sequelae is as a result of pre-existing CKD that has been unmasked, or is as a result of overt (or subclinical) iatrogenic hypothyroidism. Timing of testing and recovery of thyrotrophs and atrophic thyroid cells should be taken into consideration when interpreting the results. While it is known that overtly hypothyroid cats developing azotaemia may have reduced survival time compared to euthyroid cats following treatment, the clinical significance of azotaemia in the face of subclinical hyperthyroidism requires further examination. Until this is elucidated, azotaemic cats with subclinical hypothyroidism should be managed similarly to those with overt hypothyroidism.

There remains conflicting information in the literature regarding how SDMA changes before and after radioiodine treatment in feline hyperthyroidism and how SDMA corresponds to creatinine and TT4 concentrations at these time points. The clinical utility of SDMA as a stand-alone renal marker in cats with hyperthyroidism before and after treatment thus remains unsubstantiated.

Although SDMA and creatinine were moderately correlated after radioiodine treatment in several studies, SDMA did not correlate with GFR before and after radioiodine treatment, and the SDMA and creatinine did not agree in their classification of IRIS CKD staging. The discordance of the aforementioned studies highlights the multiple facets of SDMA metabolism that remain unexplored in the health and extra-renal disease of feline patients.

A detailed understanding of the possible biosynthesis and elimination pathways of SDMA, and how this changes in hyper-catabolic states such as hyperthyroidism is required.

Until further work is carried out to elucidate how SDMA is influenced by extra-renal factors in hyperthyroidism, SDMA is best interpreted with serial measurements and used concurrently with the classical renal biomarkers creatinine and urea.

Conflicts of interest and sources of funding

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