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1	Thyroid and Renal Function in Cats Post Low-dose (111Mbq) Radioiodine Therapy
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3 4	<b>Objectives:</b> To describe the effect of low-dose (111MBq) radioiodine therapy (RAI) on thyroid and renal function in hyperthyroid cats over a 12 month follow-up period.
5 6 7 8 9	<b>Methods:</b> Client-owned hyperthyroid cats underwent treatment with low-dose RAI and were followed for 12 months post-RAI treatment. Immediately prior to RAI treatment, and subsequently at one, six and 12 months post-RAI treatment, thyroid function was evaluated using total thyroxine (TT4) and thyroid stimulating hormone (TSH) and renal function was evaluated using serum creatinine concentration and glomerular filtration rate (GFR).
10 11 12 13 14	<b>Results:</b> Fifteen of the 24 (63%) cats achieved euthyroidism following low-dose RAI treatment. The incidence of development of overt hypothyroidism was 25% (6/24 cats). Of the cats developing overt hypothyroidism, 3/6 (50%) had decreased renal function, with decreased GFR preceding development of azotaemia in 2 out of 3 of these cats. Transient overt or subclinical hypothyroidism prior to restoration of euthyroidism was not observed in any cats.
15 16 17 18	Clinical Significance: Low-dose RAI is effective for most cats with hyperthyroidism, however, overt hypothyroidism may develop in some. Concurrent early decline in renal function may only be detected by measuring GFR rather than serum creatinine in some patients. Monitoring of patients post-RAI treatment should include TT4 and TSH with consideration of GFR measurement in non-azotaemic cats.
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20	Introduction
21 22 23 24 25	Hyperthyroidism is the most commonly diagnosed endocrinopathy in cats with a reported prevalence of 8.7% in cats over 10 years old (Stephens and others 2014). Radioactive iodine (RAI) treatment is widely considered the gold standard treatment of hyperthyroidism. The aims of RAI treatment are two-fold; firstly to cure hyperthyroidism and secondly, to prevent the development of iatrogenic hypothyroidism by administering the minimum effective RAI dose.
26 27 28 29 30	Between 15-51% of hyperthyroid cats develop azotaemia following restoration of euthyroidism (Williams and others 2010, Reinsche and others 2008). Thyroid activity directly impacts renal function; the hyperthyroid state increases glomerular filtration rate (GFR) and may consequently mask any prior loss of renal filtration function, restoration of euthyroidism reduces GFR (Boag and others, 2007) and hypothyroidism decreases GFR further (Panciera and Lefebvre, 2009).
31 32 33 34 35	Excessive thyroid suppression can lead to the development of subclinical hypothyroidism (increased thyroid stimulating hormone [TSH] concentrations with total thyroxine [TT4] concentrations within the normal reference interval) and overt hypothyroidism (increased TSH concentration and low TT4 concentrations) whilst clinical signs of hypothyroidism may not be apparent (Peterson and Becker, 1995).
36 37 38 39 40	Serum or plasma creatinine is routinely used as a marker of renal function, however, it is affected by non-renal factors, principally muscle mass. The catabolic effects of hyperthyroidism cause muscle atrophy and therefore creatinine may be an unreliable indicator of renal function in hyperthyroid cats. Additionally, endogenous creatinine production is reduced in hypothyroid dogs (Panciera and Lefebvre, 2009).
41 42 43 44 45	The greatest reduction in TT4 concentration is expected in the first month following RAI treatment (Boag and others 2007, van Hoek and others 2008). Opposing activities may occur post-RAI treatment to cause on-going changes in TT4 and TSH concentrations. These include atrophy of thyrocytes due to sublethal RAI damage resulting in a gradual decrease in TT4 concentrations (Mooney, 1994) and recovery of function of residual thyroid tissue resulting in an increase in TT4 concentrations.

- Continued change in TT4 and TSH concentrations may occur over months to years, however this has not been well documented in conjunction with renal function beyond six months in cats.
- The aim of this study was to describe the effect of low-dose (111MBq) RAI therapy on thyroid and renal function in hyperthyroid cats over a 12-month follow-up period.

# Materials and methods

Study population

Client-owned hyperthyroid cats presenting to a University referral hospital for RAI therapy were recruited prospectively into the study. The study was of observational cohort design with longitudinal follow-up. Only cats that received a low dose of 111MBq RAI were included in the study. Cats were excluded from the study if they required a different dose of RAI therapy (e.g. high dose carcinoma treatment), were not amenable to handling for repeated blood sampling, had received anti-thyroid medications within two weeks of presentation, had documented azotaemia prior to RAI therapy or were fed a restricted iodine diet. Informed consent was obtained from the owners and the study was conducted with approval from the University Animal Welfare and Ethics Review Board (UIN UB/12/025).

# Longitudinal study design

At recruitment into the study all cats were hyperthyroid. Cats were re-evaluated at one, six and 12 months post-RAI therapy. At recruitment into the study and at each subsequent time point the following were performed; full clinical examination, pertinent history, systolic blood pressure measurement by Doppler technique, blood sampling by jugular venepuncture for biochemistry and haematology and urine sampling via either cystocentesis or free catch collection.

#### Measurement of thyroid function markers

Serum TT4 was measured at a commercial reference laboratory using the Immulite 1000 chemiluminescent immunoassay. Serum TSH was measured at a commercial reference laboratory using a previously validated canine assay (Wakeling and others 2008). Thyroid function was categorised at the one, six and 12 month follow-up visits according to the following criteria: overt hypothyroid TT4 <15 nmol/l, TSH >0.15 ng/ml (Wakeling and others 2011); subclinical hypothyroid TT4  $\geq$ 15 - 60 nmol/l, TSH >0.15 ng/ml (Wakeling and others 2011); euthyroid TT4  $\leq$ 60 nmol/l, TSH  $\leq$ 0.15 ng/ml; hyperthyroid TT4 > 60 nmol/l, TSH <0.03 ng/ml.

#### Measurement of renal function markers

Glomerular filtration rate was determined using a previously described slope-intercept iohexol clearance method (Finch and others 2011). Briefly, a bolus dose of iohexol (Omnipaque<sup>TM</sup> [647mg/ml; 300mg of iodine/ml]) was administered intravenously (0.5ml/kg). Blood samples were collected at 120, 180 and 240 minutes post-injection. Iohexol concentrations were determined at an external commercial laboratory using a high performance capillary electrophoresis HPCE method<sup>iii</sup>. Clearance was determined as dose/AUC, where AUC is area under the plasma concentration versus time curve determined using a one-compartment model. A previously validated cat specific correction formula for slope-intercept clearance was applied to correct for the one compartment assumption (Finch and others 2011). In addition, serum creatinine concentrations were determined from a sample collected at the same time as GFR measurement and measured at a commercial reference laboratory<sup>i</sup>. Decreased renal function was defined as decreased GFR (<0.92 ml/min/kg; Finch, 2014) and/or azotaemia (serum creatinine >175 µmol/l, the upper limit of laboratory reference interval for feline serum creatinine).

# Data analysis

Descriptive statistics only were performed due to the small numbers of cats included in the study and the high variability between cats that would limit the statistical power if performing inferential statistics. Change in renal function over time was calculated by subtracting the measurement (serum creatinine or GFR) at one time point from the previous time point (e.g baseline – one month). The within-individual coefficient of variation (CV) % was determined from measurements in individual cats at all four time points and calculated as (SD/mean) x 100.

# Results

A total of 27 cats were recruited to the study. Twenty-five cats completed the one and six-month follow-up visit and 21 cats completed the 12-month follow-up visit. The median (range) age at recruitment to the study was 11 (7 - 16) years. Of the 27 cats, 15 were female neutered, 11 were male

neutered and one was female entire. Twenty-six cats were domestic shorthair and one was domestic longhair. One cat was excluded from longitudinal data analysis due to uncertain thyroid status. It was thought this cat may have had euthyroid sick syndrome post-RAI therapy but a final diagnosis was not available at euthanasia. Median (range) thyroid and renal function markers are presented in Table 1. At recruitment to the study all cats were hyperthyroid with normal renal function (Table 2). Fifteen (63%) cats achieved euthyroidism over the 12-month follow-up period. Two cats (8%) were persistently hyperthyroid and required second RAI treatments. Five cats (21%) classified as hyperthyroid at one-month post-RAI therapy were euthyroid by six months. Six cats (25%) developed overt hypothyroidism (two at one month, two at six months, two at 12 months) and of these cats, none regained thyroid function by the study end point or last follow-up visit. In two cats, development of overt hypothyroidism was preceded by subclinical hypothyroidism. No cats developed transient overt or transient subclinical hypothyroidism before euthyroidism, however, one cat had subclinical hypothyroidism at 12 months and it is unknown whether this resolved. A summary of the longitudinal data is presented in **Figure 1.** A total of seven cats (29%) developed decreased renal function. Of the cats that developed overt hypothyroidism (n = 6), three (50%) developed decreased renal function and one had borderline renal function (GFR 0.99 ml/min/kg, serum creatinine concentration 175 µmol/l). Decreased GFR preceded development of azotaemia in 2/3 (67%) cats. The cat with subclinical hypothyroidism at 12 months (n = 1) had decreased GFR and azotaemia at the six and 12-month revisit. Of the cats that became euthyroid (n = 15), three (20%) had decreased GFR and normal creatinine at 12 months. Of these three cats, one had decreased GFR and normal creatinine at one, six and 12 months. There was no decreased renal function in the cats that remained persistently hyperthyroid (n = 2). Mean ± SD change coefficient of variation (CV) in renal function in the hyperthyroid, euthyroid and overtly hypothyroid cats over each time point is presented in **Table 3**.

# Discussion

The present study of cats receiving low-dose (111MBq) RAI that were followed for a maximum of 12 months post-RAI therapy identified development of overt hypothyroidism in 6/24 (25%), transient overt or transient subclinical hypothyroidism before euthyroidism in 0% and persistent hyperthyroidism in 2/24 (8%). All of the cats with subclinical hypothyroidism progressed to overt hypothyroidism however, one cat (4%) developed subclinical hypothyroidism at the 12-month time point and it is unknown whether this progressed to overt hypothyroidism or resolved. Of the six cats that developed overt hypothyroidism, three (50%) developed decreased renal function, with decreased GFR preceding azotaemia in 2/3 (67%) cats.

Variable RAI dosing enables individual dosing tailored to the patient, although this is not used in all clinics treating cats with RAI; this study evaluated a standard fixed 'low' dose of 111MBq that was used to treat cats at the clinic (however, since completion of the study, the protocol at the clinic has changed to employ variable dosing). Published scoring schedules use the severity of hyperthyroid clinical signs, TT4 concentrations and goiter size to guide doses, with low doses previously classed as 74-130MBq and 80-120MBq (Mooney, 1994; Peterson and Becker, 1995). In addition, some clinics use scintigraphy for thyroid gland volume estimation to guide doses, however the optimal method is undecided (Morre and others 2018).

A recent study comparing low (defined as 74 MBq) and standard dose (defined as 148 MBq) RAI treatment for hyperthyroidism in cats reported the incidence of overt hypothyroidism to be 18% with standard dose RAI and 1% with low dose RAI. It is important to note that a higher cut off for TSH to define overt hypothyroidism was used compared to the present study (0.3 ng/ml versus 0.15 ng/ml) (Lucy and others 2017). In the same study, the incidence of subclinical hypothyroidism was 46% in cats treated with standard dose RAI and 21% in cats treated with low dose RAI. In the present study, the incidence of development of overt hypothyroidism was higher (25%) and subclinical hypothyroidism lower (4%). In two out of six (33%) of the cats that developed overt hypothyroidism in the present study, it was preceded by subclinical hypothyroidism. Therefore, although the earlier study (Lucy and others 2017) reported a much higher incidence of subclinical hypothyroidism, the study period was only six months and it is possible that had the cats been followed longer, they could have progressed to overt hypothyroidism. Conversely, 4/6 overtly hypothyroid cats in the present study could be classed as mildly hyperthyroid at baseline (Petersen and Becker 1995), and these cats were potentially excessively treated with 111MBq. Indeed, 111MBq may not be considered 'low-dose' when compared to low doses used in other studies. The incidence of development of overt hypothyroidism

(25%) in the present study is in line with that of cats receiving medical management alone or in combination with thyroidectomy (**See Table 4**). The incidence of development of subclinical hypothyroidism (4%) is in line with the study by Williams and others (Williams and others 2010a) but lower than the studies by Aldridge and others (Aldridge and others 2015) and Lucy and others (Lucy and others 2017) (**See Table 4**). Differences in the incidence of subclinical and overt hypothyroidism may partly be explained by the use of different assays to measure TSH in the studies and also the upper reference limit of TSH and lower limit for TT4 used to define a cat as being hypothyroid (subclinical or overt). Standardisation of both measurement of TSH and the definition of subclinical and overt hypothyroidism would be helpful for on-going research into this important and evolving area of feline hyperthyroid management.

In the present study, 4/6 (67%) of cats that developed overt hypothyroidism did so within the first six months post-RAI therapy. Spontaneous recovery of thyroid function was not observed in any of the overtly hypothyroid cats. In human patients developing hypothyroidism post-RAI, 86% do so in the first 6 months and the rate is low after 12 months (3%/year) (Peacey and others 2012). Changes in thyroid function in cats may occur longer than 12 months post-RAI therapy. Normalization of TSH and TT4 has been reported over 3-21 months (median 6 months) and development of hypothyroidism after 18 months (Peterson and Rishniw, 2017). The rate of development of overt or subclinical hypothyroidism and also recovery of thyroid function beyond 12 months in cats warrants further studies.

Previous studies have reported the incidence of development of azotaemia within six months of initiating medical management, RAI therapy or thyroidectomy for hyperthyroidism to be between 15% and 51% (Becker and others 2000, Boag and others 2007, Graves and others 1994, Lucy and others 2017, Williams and others 2010a, Williams and others 2010b, Reinsche et al, 2008). In a previous study of cats treated with standard dose RAI (148MBq) the incidence of azotaemia was 46% versus 29% in cats treated with low dose RAI (74MBq) (Lucy and others 2017). In cats with normal renal and thyroid function at baseline, the incidence of development of azotaemia over 12 months is reported to be between 11% (Finch and others 2016) and 30.5% (Jepson and others 2009). The present study found the incidence of reduced renal function over 12 months to be 29%. Cats with iatrogenic hypothyroidism are at increased risk of developing azotaemia compared to cats that remain euthyroid (Williams and others 2010a). Of the overtly hypothyroid cats in the present study, 50% had reduced renal function compared to 20% of euthyroid cats. In the overtly hypothyroid cats, decreased GFR preceded development of azotaemia in 2/3 of the cats. However, as one of the hypothyroid cats had both decreased GFR and azotaemia at the one-month time point when first identified to be overtly hypothyroid, it is unknown whether a decline in GFR preceded azotaemia in this cat and therefore, it is possible up to 100% of the overtly hypothyroid cats had a decline in GFR prior to development of azotaemia. Of all of the cats in the study with reduced renal function, 71% remained non-azotaemic despite having reduced GFR. These findings are unsurprising given the lack of sensitivity of creatinine at detecting early decline in renal function (Finch 2014). However, in cats with hypothyroidism, decreased endogenous creatinine production may also influence circulating creatinine concentrations. This has been shown in dogs with experimentally induced hypothyroidism (Panciera and Lefebvre 2009). The present study highlights the importance of measuring GFR rather than serum creatinine concentration to accurately assess renal function in non-azotaemic cats with the potential to be hypothyroid. Further studies are required exploring other markers of GFR such as SDMA.

The largest change in renal function was seen in the first month following RAI (see **Table 3**) and this is in line with findings reported in previous studies (Boag and others 2007, van Hoek and others 2008). The greatest within-individual variation in renal function over time occurred in the overtly hypothyroid cats (see **Table 3**). This likely reflects that this was the group with the largest number of cats with a decrease in renal function. A recent study reported the mean within-individual CV for GFR and serum creatinine concentration to be 28.94 and 8.82% respectively in non-azotaemic cats and 19.98 and 6.81% in azotaemic cats (Finch and others 2018). It is interesting that the within-individual variation for serum creatinine concentration was lower in the previous study compared to the present study. This may reflect differences in the reference laboratories used to measure serum creatinine concentration or may suggest there is greater variability in serum creatinine concentration in previously hyperthyroid cats treated with RAI compared to euthyroid cats. Greater variability in serum creatinine is not unexpected in cats that were previously hyperthyroid as change in muscle mass in such cats will be

associated with change in endogenous creatinine production

Correction of iatrogenic hypothyroidism resolved azotaemia in 50% of cats (Williams and others 2014). However, given that 2/3 (67%) of hypothyroid cats with decreased GFR were non-azotaemic in the present study, it is possible that many cats with resolved azotaemia may still have reduced renal function that is not detected by measuring serum creatinine concentration alone. Indeed, changes in creatinine concentrations may simply be related to changes in endogenous creatinine production. Hyperthyroid cats have been reported not to regain normal muscle mass following treatment for hyperthyroidism, thus impacting on endogenous creatinine concentration (Peterson and others 2016). Therefore, measurement of GFR may prove to be important in not only defining renal function and guiding management of cats with iatrogenic hypothyroidism but also in monitoring renal function once management has been initiated. Development of kidney disease is a predictor of negative outcome following RAI therapy in cats (Slater and others 2001) and cats with iatrogenic hypothyroidism that develop azotaemia have reduced survival compared to non-azotaemic cats without iatrogenic hypothyroidism (Williams and others 2010a). Therefore, identifying a decline in renal function early in cats with iatrogenic hypothyroidism and initiating appropriate management such as L-thyroxine is also likely to be important in improving prognosis.

In the present study, two cats (8%) remained persistently hyperthyroid despite partial responses necessitating second RAI treatments. This is comparable to a six-month prevalence of hyperthyroidism of 7% reported by Morre and others in a group of cats also treated with 111MBq RAI (Morre and others 2018). Of the two cats that remained persistently hyperthyroid in the present study, one had a very high TT4 concentration pre-RAI (351 nmol/l) whilst the other hyperthyroid cat along with the remainder of the cats in the study had TT4 <250 nmol/l. Based on this and unpublished data from cats undergoing RAI therapy at the University referral hospital, the authors recommend that low dose RAI (111MBq) be reserved for cats with mild to moderate hyperthyroidism (i.e. TT4 <250nmol/l).

The present study has a number of limitations. Firstly, the small numbers of cats included in the study. Secondly, the follow-up period of only 12 months. However, this is the first study to provide data from cats receiving RAI therapy for longer than six months follow-up using TSH in conjunction with TT4 concentrations to define thyroid status and GFR to assess renal function. Finally, the use of iohexol clearance for GFR measurement prior to RAI therapy. Iodine containing contrast agents may interfere with thyroid uptake of RAI. However, it has been shown that although cats pretreated with iohexol as part of GFR measurement have decreased uptake of RAI, the effective half-life of RAI and therapy outcome do not differ from cats not pretreated with iohexol (Peremans and others 2008).

To conclude, low dose (111MBq) RAI was associated with an incidence of development of overt hypothyroidism of 25%. Thyroid function including TT4 and TSH should be monitored longer-term in all cats that have undergone RAI as hypothyroidism can develop at variable rates in the first year post treatment. In addition, renal function should ideally be monitored by GFR in non-azotaemic cats to ensure early and accurate detection of any decline, particularly in cats with the potential to develop hypothyroidism.

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- ii) Royal Veterinary College Diagnostic Laboratory Services, Hawkshead, Hertfordshire, UK
- iii) DeltaDOT Ltd, London BioScience Innovation Centre, London, UK

No conflict of interest has been declared

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