ASSESSMENT OF RENAL FUNCTION IN HYPERTHYROID CATS MANAGED WITH A CONTROLLED IODINE DIET

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Abstract

Hyperthyroidism is the most common endocrinopathy of geriatric cats and has physiologic effects on almost every organ in the body. It specifically affects the kidneys by increasing renal blood flow and glomerular filtration rate. In addition, activation of the renin angiotensin aldosterone system (RAAS) is increased and ultimately leads to efferent glomerular arteriole constriction and potentially glomerular hypertension. The classic treatment modalities for feline hyperthyroidism (anti-thyroid medication, radioiodine or surgery) have been evaluated for their overall effects on renal function. Studies have demonstrated that glomerular filtration rate (GFR) declines and serum creatinine increases with hyperthyroid treatment independent of the treatment modality. Hill's® Prescription Diet® y/d® Feline, a relatively new dietary treatment modality for feline hyperthyroidism with controlled iodine concentrations, reduced phosphorus and protein, and increased omega-3 fatty acids, has been shown to significantly decrease thyroid hormone levels. The research provided in this report is the first evaluating the posttreatment effects of y/d® Feline on renal function. In agreement with previous studies, our research found that y/d® Feline resulted in a significant decrease in thyroid hormone levels. However, in contrast to other treatment modalities, y/d® Feline did not result in a significant decline in GFR, and it did result in a significant decline in mean serum creatinine concentration. These data indicate that y/d® Feline, as a treatment for feline hyperthyroidism, does not have a negative effect on renal function.

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Feline Hyperthyroidism Introduction

The clinical condition of feline hyperthyroidism occurs due to excessive production and secretion of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Hyperthyroidism was first described in human beings in 1913, and in cats in 1979.[1] Most hyperthyroid cats (70%) have benign adenomatous disease of both thyroid glands,[2] and a minority (<5%) have a malignant thyroid carcinoma.[3]

Etiology of Feline Hyperthyroidism

The etiology of feline hyperthyroidism remains incompletely understood. Due to the increasing prevalence of feline hyperthyroidism since the syndrome was first identified, the possible contributions of immunologic, nutritional, environmental, and genetic factors have been extensively evaluated. In human beings, hyperthyroidism is typically associated with autoimmune disease (Graves' disease), and a similar etiology has been investigated in cats. Although some hyperthyroid cats have been found to have autoantibodies mimicking thyroid stimulating hormone (TSH) that may contribute to the development of hyperthyroidism,[4] other investigators have not been able to verify this finding.[5,6] Other studies have suggested an increased prevalence of hyperthyroidism in cats fed mostly canned food, or specifically canned foods with fish or liver and giblets-flavors.[7,8,9,10] Environmental factors that have been implicated include soy isoflavones, phthalates, resorcinol, polyphenols and polychlorinated biphenyls, some of which are considered goitrogens and others of which can be found in the environment or commercial cat foods.[11,12] Additionally, cats that live primarily indoors, and those that have regular exposure to flea sprays, fertilizers, pesticides, or insecticides have been found to have an increased prevalence of hyperthyroidism, while Siamese, Himalayan and

purebred cats have been reported to have a decreased risk for hyperthyroidism.[7,10,11] A direct cause and effect between the above factors and the development of hyperthyroidism remains difficult to prove.

Clinical Presentation of Feline Hyperthyroidism

Cats that are affected by hyperthyroidism have a mean age of 12-13 years old, with less than 5% being less than 10 years of age.[13] The prevalence of hyperthyroidism in a population of cats greater than nine years of age was recently reported to be 6%.[14] The diagnosis of feline hyperthyroidism involves consideration of clinical signs, physical exam findings, as well as clinicopathologic changes and specific confirmatory testing. Because thyroid hormones have multiple actions throughout the body, almost every organ system is affected by elevations in thyroid hormone concentrations. Classically, cats that exhibit clinical evidence of thyrotoxicosis have a history of weight loss in the face of a normal or increased appetite, increased activity/restlessness, polyuria/polydipsia, unkempt hair coat, and gastrointestinal signs such as vomiting and diarrhea.[2,13,15,16] However, the severity of reported signs have decreased in the past 20 years as the syndrome is recognized earlier in the course of disease, presumably due to increased awareness.[2,13,15,16] In addition, approximately 10% of affected cats will exhibit so-called 'apathetic hyperthyroidism', which is characterized by decreased appetite and lethargy.[2,15] More than 90% of hyperthyroid cats have a palpable thyroid nodule at the time of diagnosis. Elevation in thyroid hormone concentration also causes alterations in cardiovascular hemodynamics, affecting heart rate, heart rhythm and cardiac output.[16,17,18] In hyperthyroid cats this can be appreciated clinical by the presence of tachycardia, increased heartbeat intensity, and arrhythmias as well as a systolic heart murmur (usually grade I-III/VI), which occurs in

approximately 50% of hyperthyroid cats.[2,13,15] Although these may be common findings on physical exam, congestive heart failure is less common.[2,13] Finally, mild to moderate hypertension was originally thought to be a common finding in hyperthyroid cats, which would resolve with return to a euthyroid state. Current reports indicate that approximately 10% of cats are reported to have hypertension at the time of diagnosis of hyperthyroidism,[19] which is associated with a reduced survival time in affected cats.[20] An additional 20% of cats develop hypertension following treatment and return to a euthyroid state, which may be associated with the unmasking of renal dysfunction.[19,21]

Hematologic and biochemical abnormalities are common with hyperthyroidism. Approximately 40-50% of cats with hyperthyroidism exhibit slight elevations of the packed cell volume (PCV), and approximately 20% develop a macrocytosis.[2,13] Erythrocyte changes are thought to result from an increase in erythropoietin production secondary to the increase in oxygen consumption that occurs in hyperthyroidism, as well as the direct effect on the bone marrow by thyroid hormone-mediated β-adrenergic stimulation to increase production and release of red blood cells.[22] Common leukogram changes include neutrophilia, lymphopenia, eosinopenia, and monocytosis.[13,15] The most common biochemical changes observed in hyperthyroid cats are increased activities of aminotransferase (ALT) and alkaline phosphatase (ALP). In fact, greater than 90% of hyperthyroid cats have an elevation in either ALT or ALP.[2,13,15] Although elevations in both ALT and/or ALP are typically mild, severe elevations can be observed. There is little data regarding the mechanism for liver enzyme elevations in cats with hyperthyroidism, however, in hyperthyroid rats, a direct toxic effect of T_3 resulted in lipid peroxidation, protein oxidation, and glutathione depletion of hepatic mitochondria with subsequent apoptosis has been observed.[23,24] Limited feline studies have shown that both the

liver and bone ALP isoenzymes contribute to serum ALP elevations in hyperthyroid cats.[25,26,27] Although previous recommendations included evaluating hyperthyroid cats with ALP or ALT activities greater than 500 IU/L for concurrent disease,[2,13,15] further investigation has revealed that the changes experienced by the liver secondary to hyperthyroidism usually do not affect liver function tests, such as paired serum bile acids, and thus such testing may not be warranted.[28] In addition, histologic evaluation of liver samples from cats with hyperthyroidism reveal nonspecific and mild changes, and liver enzyme changes associated with hyperthyroidism usually return to within the reference interval with successful management of hyperthyroidism.[29]

Urinalysis results of hyperthyroid cats are generally nonspecific, however many hyperthyroid cats have mild proteinuria. Although the mechanism of proteinuria in hyperthyroid cats is incompletely understood, successful treatment of hyperthyroidism leads to a decrease in urinary protein excretion as assessed by urine protein to urine creatinine (UPC) ratio.[30] It has also been reported that up to 12-22% of hyperthyroid cats present with urinary tract infections.[31,32] When signalment, history, clinical signs, physical exam findings, and initial blood screenings are compatible with feline hyperthyroidism, additional confirmatory testing is recommended.

Specific Thyroid Function Tests

Total T_4 Concentration

Although T_3 is the biologically active form of thyroid hormone, T_4 is the primary hormone secreted from the thyroid gland and found in the circulation and is later metabolized to T_3 in peripheral tissues.[33,34] Although total T_4 (TT_4) concentrations vary considerably throughout the day in hyperthyroid cats, more than 90% of hyperthyroid cats will be confirmed via random

serum TT_4 testing.[13,15,35] In contrast, over 25% of hyperthyroid cats will have a serum total T_3 (TT_3) concentration within the reference interval.[13,35] Thus, measurement of circulating serum TT_4 concentration is superior to measurement of serum TT_3 concentration for identifying cats with hyperthyroidism, and is the initial screening test of choice.[15,36,37] Furthermore, simultaneous measurement of TT_3 and TT_4 concentrations does not offer a diagnostic advantage over TT_4 measurement alone.[13,35,37]

Serum TT_4 concentration measures the protein-bound and free hormone fractions. T_4 is highly protein bound and the free (unbound) fraction makes up less than 1% of the circulating pool. Radioimmunoassay (RIA) is the gold standard method for measurement of serum TT_4, but methodology limitations associated with RIA has prompted validation of other assay methods including a homogenous enzyme immunoassay and chemiluminescent enzyme immunoassay (CLEIA).[35,38,39,40] The availability of these methods varies based on the laboratory used. In addition, a commercial semiquantitative ELISA T_4 kit is available for in-house use. The ELISA method has the advantage of providing instant results to the practitioner, and is accurate when compared to the RIA method.[40] Overall, each of these tests has pros and cons; the test chosen should be based on the turn around time needed and test availability.

Due to fluctuations of thyroid hormones in the circulation, the TT_4 concentration of cats with early or mild hyperthyroidism may fall within the reference interval. Furthermore, certain drugs and non-thyroidal disorders can suppress total thyroid hormone concentrations. Mechanisms for TT_4 suppression include altered thyroid hormone metabolism, altered T_4 binding within cells or to plasma carrier proteins, and altered transport of T_4 into cells.[41] Of hyperthyroid cats with the TT_4 concentration within the reference interval, approximately 20-30% have concurrent illness and the remaining 70-80% likely have early disease.[35] Thus, if a single,

random serum TT_4 concentration is within the reference interval, yet the cat has historical, physical exam, and laboratory changes compatible with hyperthyroidism, the TT_4 concentration should be reevaluated after several weeks, in addition to ruling out and/or treating any nonthyroidal illness.[38] If non-thyroidal illness has been ruled-out and a repeat TT_4 remains within the reference interval, performing a serum free T_4 (fT_4) assay is recommended.

Free T_4 Concentration

Serum fT_4, the unbound fraction of T_4 hormone, represents less than 1% of total circulating thyroid hormone. FT_4 is the only T_4 fraction that can diffuse across cell membranes and serves as a "prohormone" for T_3.[34] Serum fT_4 is a more sensitive test for hyperthyroidism than the serum TT_4. Greater than 95% of hyperthyroid cats that have a TT_4 concentration within the reference interval will have an elevated fT_4 concentration.[35] It is generally accepted that cats without non-thyroidal illness that have a TT_4 concentration in the upper third of the reference interval, an elevated fT_4 concentration and compatible clinical signs, are likely hyperthyroid.[42] fT_4 concentration is also affected by non-thyroidal factors, which can cause a false elevation in fT_4. The mechanism for elevation of circulating fT_4 during nonthyroidal disease is not completely known, but has been speculated to be due to impaired clearance of fT_4 from the serum[33]. Up to 12% of euthyroid cats may have an elevated fT_4 concentration due to nonthyroidal illness, making measurement of fT_4 less specific for hyperthyroid diagnosis than TT_4.[35,41,43] For this reason, fT_4 should not be used as the sole test for the diagnosis of hyperthyroidism. Finally, hyperthyroid cats with an elevated TT_4 concentration will always have a concurrent elevation in the fT_4 concentration. Therefore, measurement of fT_4 is not indicated or necessary if the TT_4 is elevated.[35] If TT_4 and fT_4 concentrations are found within the

reference interval on several separate occasions, but clinical suspicion of hyperthyroidism remains high, additional testing (e.g. T_3 suppression test, thyrotropin-releasing hormone (TRH) stimulation test, thyroid-stimulating hormone (TSH) response test, thyroid scintigraphy) should be considered.

T_3 Suppression Test

The T_3 suppression test evaluates the integrity of the physiological feedback loop by which thyroid hormone regulates pituitary gland function. In normal cats, thyroid hormone exerts negative feedback on the hypothalamus and anterior pituitary and leads to decreased secretion of TRH and TSH, respectively, until inhibition is released by a fall in circulating thyroid hormone concentrations. The T_3 suppression test works according to the principle that administration of exogenous T_3 to a cat with normal thyroid function suppresses pituitary TSH secretion and leads to a decrease in endogenous T_4 secretion. Cats with primary hyperthyroidism, however, secrete thyroid hormones independent of pituitary control. In contrast with normal cats, TSH secretion is chronically suppressed during primary hyperthyroidism and exogenous T_3 administration has little to no effect on endogenous serum TT_4 concentrations. The T_3 suppression test is helpful in distinguishing mildly hyperthyroid cats from euthyroid cats; however, it requires multiple days of treatment for suppression to occur and owner compliance is critical. Following collection of baseline serum TT_3 and TT_4 samples, owners are instructed to administer T_3 hormone (liothyronine; Cytomel) at 25µg orally three times daily for two days, and once on the morning of day 3, for a total of 7 doses.[44] Two to four hours after the final dose is given, TT_3 and TT_4 concentrations are assessed. The pre- and post-liothyronine samples should be submitted to the laboratory at the same time to limit the influence

of interassay variation. Cats with hyperthyroidism will have little to no decrease in TT_4 concentration after liothyronine administration, while suppression of TT_4 concentration of 50% or more will occur in euthyroid cats.[44] Lack of TT_4 suppression could also be due to poor compliance with the testing protocol, which can lead to a false positive result. Compliance can be gauged by comparing TT_3 concentrations before and after the test. If the liothyronine was administered correctly, the final TT_3 concentration will be elevated above the initial sample. If this does not occur, owner compliance should be questioned, and the test result should be considered invalid.

TRH-Stimulation Test

The TRH-stimulation test also evaluates the integrity of the pituitary-thyroid gland feedback system via administration of TRH. TRH from the hypothalamus stimulates release of TSH from the anterior pituitary gland to increase synthesis and release of thyroid hormones from the thyroid gland. Administration of exogenous TRH to cat with normal thyroid function will increase TSH secretion and increase serum TT_4 concentrations. To perform a TRH-stimulation test, a serum TT_4 sample is collected before and 4 hours after intravenous administration of 0.1mg/kg TRH.[45] Cats with even mild hyperthyroidism should have little (<50%) or no increase in serum TT_4 concentration due to hyperthyroid-induced chronic suppression of endogenous TSH. Clinically healthy cats, and cats with nonthyroidal disease should have an increase in serum TT_4 concentrations of greater than 60%.[45] This test is considered as reliable as a T_3 suppression test, however, the only FDA-approved preparation of TRH is no longer available, side effects are common following TRH administration,[45] and results can be difficult to

determine especially in cats with concurrent illness,[46] thus, generally this test is not recommended.

TSH-Response Test

A TSH-response test is typically utilized to aid in the diagnosis of hypothyroidism in dogs, but has the potential to differentiate euthyroid cats from those with hyperthyroidism as well. The protocol involves obtaining a baseline serum TT_4 value, followed by administration of TSH, and measure of TT_4 6-8 hours later. Hyperthyroid cats should have little or no response to exogenous TSH administration, however, results can be difficult to interpret due to overlap in TT_4 response in euthyroid and hyperthyroid cats.[29,37,41] In addition, the bovine TSH initially utilized for this test is no longer available, and the response to administration of recombinant human TSH has not been evaluated in hyperthyroid cats. Therefore, this test is not currently recommended for the diagnosis of hyperthyroidism.[29,37,41]

Random TSH Concentration Testing

Measuring a random circulating TSH concentration to detect subclinical hyperthyroidism may be a helpful tool. Cats with subclinical hyperthyroidism should have a low circulating TSH concentration before elevation in TT_4 occurs.[14] When evaluating hyperthyroid cats, normal cats, and cats with CKD, it was found that all hyperthyroid cats had TSH values below the quantification value.[41] However, 5 out of 40 non-hyperthyroid cats also had TSH levels below the quantification value, but the presence of CKD did not appear to affect TSH concentrations.[41] Furthermore, in 104 client-owned cats, TSH concentrations were evaluated with the hypothesis that euthyroid geriatric cats with undetectable TSH concentrations would have an increased risk

of developing clinical hyperthyroidism.[14] Although the cats with undetectable baseline TSH concentrations were significantly more likely to be diagnosed with hyperthyroidism within 14 months, only about half of the cats with undetectable baseline TSH concentrations became hyperthyroid within the 14-month study period.[14] Ultimately, further studies are needed to determine the diagnostic utility of a random TSH concentration in cats.

Thyroid Scintigraphy

If results of thyroid hormone tests are equivocal but clinical suspicion remains high, thyroid scintigraphy should be considered to confirm hyperthyroidism. In addition to confirming hyperthyroidism, thyroid scintigraphy can also provide information that aids in treatment decisions, and is the best way to detect metastasis of malignant thyroid tumors. Multiple radionuclides have been utilized for imaging the thyroid glands. The use of radioactive iodine (^{131}I, or ^{123}I) has been described, however radioactive technetium-99m (pertechnetate; $^{99m}TcO_4$) is the radionuclide most commonly used. $^{99m}TcO_4$ is trapped and concentrated within thyroid follicular cells because $^{99m}TcO_4$ molecular configuration mimics the size and charge of iodide.[47] $^{99m}TcO_4$ is the radionuclide of choice for routine thyroid imaging due to its low-cost, short half-life, rapid uptake by the thyroid, low-energy γ-particle emission, and lack of β-emission.[47] After IV injection, $^{99m}TcO_4$, concentration within the thyroid tissue occurs over 20-120 minutes and all functioning thyroid tissue can be detected using a gamma camera.[2,47,48,49] In normal cats, $^{99m}TcO_4$ concentrates in salivary and thyroid tissue to a similar degree and to a lesser degree in epithelial tissues such as the gastric mucosa.[47] The normal thyroid glands are elongate ovals of similar size and location. Thyroid activity is assessed by comparing the ratio of $^{99m}TcO_4$ uptake by the thyroid gland with uptake by the zygomatic-molar salivary gland using a region of interest

drawn to include salivary and thyroid tissue. The thyroid: salivary gland uptake ratio is approximately 1: 1 in normal cats and greater than 1:1 in hyperthyroidism.[47,48] The increase in thyroid: salivary ratio is directly proportional to thyroid gland function.[48]

As previously discussed, most hyperthyroid cats have bilateral disease, even if not appreciated with thyroid palpation. Thyroid scintigraphy allows the extent of abnormal thyroid tissue to be determined. Scintigraphy of cats with true unilateral thyroid disease will reveal only one active thyroid gland because chronic TSH suppression leads to atrophy of the contralateral gland. In contrast, both thyroid glands are detected in cats with bilateral disease, despite the lack of circulating TSH. Bilateral hyperthyroidism typically results in asymmetric thyroid enlargement. The literature has reported that 3%-20% of hyperthyroid cats have abnormal functional thyroid tissue located in the cranial mediastinum, which can only be detected with scintigraphy.[50] Histopathology remains the gold standard for the diagnosis of thyroid carcinoma, however, thyroid scintigraphy can aid in the presumptive diagnosis via detection of masses that cannot be palpated. Although one report found no reliable features on scintigraphy to distinguish thyroid carcinoma from adenoma,[51] others have described associations between malignancy and certain radionuclide uptake patterns: uptake in the cranial mediastinum; detection of multiple and extensive regions of uptake; distorted, irregular uptake with activity extending beyond the thyroid gland margins; and detection of linear multifocal uptake patterns.[52,53,54]

Thyroid Ultrasound

Ultrasonography can be utilized to evaluate the architecture of the thyroid glands, however, it is not useful for the diagnosis of hyperthyroidism. The normal feline thyroid gland is thin, fusiform-shaped, approximately 15-25mm in length, with uniform echogenicity, surrounded

by a thin, hyperechoic capsule.[55] Thyroid ultrasound examination of 15 hyperthyroid cats revealed thyroid glands that were larger with rounded margins, mixed echotexture, and increased vascularity compared to the appearance of the same glands 6 months after successful ^{131}I therapy.[56] Sonographically determined volumes of single adenomatous glands from hyperthyroid cats ranged from 552-572mm^3 compared with thyroid volumes ranging from 40-140mm^3 determined using cats with normal thyroid function.[56,57]

Treatment Options for Feline Hyperthyroidism

The major modalities currently available for the treatment of cats with hyperthyroidism include non-curative therapy via medical management with methimazole (Tapazole) and dietary management with Hill's® Prescription Diet® y/d® Feline, or curative therapy with surgery (thyroidectomy) and/or radioactive therapy (^{131}I). Each treatment modality has advantages and disadvantages and the treatment decisions should be based on the needs of each individual cat and owner.

Methimazole

Medical management with oral methimazole is a commonly used non-curative treatment modality in the United States. Oral methimazole therapy provides an opportunity to adjust dosage of anti-thyroid medication over time as needed, however non-curative treatment necessitates daily life-long administration of medication to control hyperthyroidism. Methimazole is a thiourylene compound that blocks the synthesis of thyroid hormones by inhibiting thyroid peroxidase activity, leading to reduced organification of iodide, as well as inhibition of the coupling of iodothyronines to form T_3 and T_4.[58] Methimazole does not inhibit

the release of preformed, stored thyroid hormone, which delays the normalization of T_4 concentrations by 2-4 weeks after initiating therapy.[36] Methimazole has a serum half-life of 2.3 hours in hyperthyroid cats and 4.7 hours in normal cats.[58,59] Carbimazole, another antithyroid medication is metabolized to methimazole after oral administration making it equally effective as methimazole. Carbimazole is widely used in Europe and Asia for treatment of feline hyperthyroidism but is not licensed for use in the United States.[29]

Evaluation of 262 hyperthyroid cats treated with methimazole as the sole therapy, revealed a decrease in TT_4 concentration after 2-3 weeks of therapy.[36] Side effects associated with oral methimazole were reported in approximately 18% of treated cats and included vomiting, anorexia, depression, and self-induced excoriations of the face or neck, blood dyscrasias and hepatopathy.[36] These effects are typically observed within 2-4 weeks of initiation of methimazole therapy. If less severe side effects such as vomiting are observed, a decrease in methimazole dose can be attempted, however if the more serious blood dyscrasias or hepatopathy occur, the use of methimazole should be discontinued immediately, and supportive care should be instituted as necessary.

The recommended starting dose is 2.5mg methimazole per os twice daily.[60] Although once daily dosing has been advocated, twice daily dosing has been found to be more effective.[61] After 2-3 weeks on the starting dose, the serum TT_4 should be determined; the target TT_4 concentration is in the lower half of the reference interval.[60,61] A recent study determined that the timing of blood collection after methimazole administration is not crucial and does not affect the ability to assess the therapeutic response.[62] Continued monitoring of TT_4 concentrations should occur every 2-3 weeks after a dosage change, 3 months after initial stabilization of TT_4, and then every 6 months.[60] If the recheck serum TT_4 concentration is within, or just above, the

reference interval, the dose should be maintained. If the serum TT_4 concentration is below the reference interval, a dose reduction of 2.5 mg per day is indicated.[60] If serum TT_4 remains significantly elevated despite therapy, compliance should first be assessed and if judged adequate, the methimazole dose should be increased by 2.5mg per day.[60] Although the effects of methimazole on TT_4 values are typically observed within the first week of therapy initiation, resolution of clinical signs may not be observed for up to 6 weeks after euthyroidism is restored.

Hyperthyroid cats with concurrent chronic kidney disease (CKD) can present a treatment dilemma. Multiple studies have confirmed that treatment of hyperthyroidism with methimazole (as well as ^{131}I and thyroidectomy) decreases glomerular filtration rate (GFR).[63,64,65] Although the decrease in GFR is a result of return to a euthyroid state rather than a consequence of the particular anti-thyroid therapy used, the decreased renal excretion can either unmask previously undiagnosed CKD, or exacerbate known CKD. In non-azotemic cats with unrecognized early CKD, it remains difficult to predict the magnitude of the GFR decrease or the development of azotemia following successful treatment of hyperthyroidism. For this reason, it is historically recommended that treatment of cats with previously diagnosed renal disease start at a lower dose of methimazole, such as 1.25mg twice daily or 2.5mg once daily. In addition, a trial with oral methimazole is often recommended prior to pursuit of either thyroidectomy or ^{131}I to assess possible adverse renal function effects after restoration of euthyroidism.

During oral methimazole therapy, most cats exhibit only mild changes in renal function (<30% increase in serum creatinine), which stabilizes within approximately one month after successful treatment of hyperthyroidism.[64,65] In addition, although it is not uncommon for cats to experience azotemia after successful treatment of hyperthyroidism, it has been shown that those cats that develop azotemia post-methimazole or I^{131} therapy do not have a decreased overall

survival time compared with hyperthyroid-treated cats that remain nonazotemic.[66] There is increasing evidence that maintenance of a hyperthyroid state is detrimental to long-term renal function. For example, when evaluating the *N*-acetyl-β-D-glucosaminidase index (NAG_i), a specific marker of active proximal tubular damage, in 24 nonazotemic hyperthyroid cats treated with methimazole, the high levels of NAG_i in hyperthyroid cats decreased following therapy, indicating the renal changes associated with hyperthyroidism can be reversed.[67] Therefore, despite the risk for reduced renal function, maintaining TT_4 concentration in the lower half of the reference interval is indicated for affected cats unless there is a profound increase in azotemia that adversely affects the cat's quality of life.

Although post-therapy azotemia has not been associated with decreased survival times, cats with hyperthyroidism and evidence of preexisting CKD treated with oral methimazole or ^{131}I had significantly shorter survival times than hyperthyroid cats that did not have evidence of renal disease.[68] Overall, the median survival time of cats treated with methimazole alone has been reported as approximately 2 years, while those treated with methimazole followed by ^{131}I had a median survival time of 5.3 years.[68] Another study of 300 hyperthyroid cats treated with oral methimazole or carbimazole alone or in combination with thyroidectomy found the overall median survival time to be 417 days.[20] Of these 300 cats, the azotemic hyperthyroid cats had a significantly shorter median survival time (178 days) than non-azotemic cats (612 days).[20]

In addition to oral methimazole, compounded topical preparations of methimazole are available that are absorbed transdermally. Initial studies reported the bioavailability of transdermal methimazole to be poor after application of a single dose applied to the pinnae of healthy cats.[69] However, long-term use of topical methimazole decreased TT_4 concentrations and resulted in a restored euthyroidism.[69] Although the overall efficacy of transdermal

methimazole was less than oral methimazole, and oral methimazole was significantly more effective than the transdermal formulation at two weeks post-therapy, by four weeks post-therapy the initial difference in TT_4 concentrations was no longer significant.[71] This data suggests that chronic use of transdermal methimazole can be effective in lowering TT_4 concentrations.[71] The recommended initial dose of the transdermal formulation is 5-10mg per cat, and once daily application appears to be as effective in controlling TT_4 as twice-daily application.[72,73] Gastrointestinal side effects were found to occur less frequently with the transdermal formulation compared with the oral formulation.[71] Additional adverse effects associated with the transdermal formulation include mild crusting and erythema at the site of application. Overall, transdermal methimazole may be a viable option for some patients, but it must be remembered that whenever using compounded medications, that different compounded products can vary in efficacy and safety.

Hill's® Prescription Diet® y/d® Feline

The use of a controlled-iodine diet is a newly developed therapy for feline hyperthyroidism. The only commercial iodine-controlled diet available for the management of feline hyperthyroidism is Hill's® Prescription Diet® y/d® Feline. Iodine is the major mineral component of thyroid hormones and its only known biologic function is in the synthesis of T_3 and T_4 hormones.[34] Iodine content in commercial cat foods varies widely, ranging from undetectable, to greater than 35 parts per million (ppm). Absolute dietary iodine requirements for cats are unknown, and the precise requirements are difficult to determine since the thyroid gland is able to adapt to wide variations in iodine intake.[34] In addition, other dietary ingredients such as perchlorate can interfere with thyroid usage of iodine and iodine measurements by

analytical methods.[34] y/d® Feline has a reduced iodine content, allowing decreased thyroid hormone production, and requires strict dietary compliance for successful management of hyperthyroidism. Concurrent use of this diet and methimazole is not recommended.

The effects of dietary iodine restriction on the thyroid gland were evaluated by feeding 9 cats with naturally occurring hyperthyroidism diets containing either 0.47 ppm, 0.28 ppm, or 0.17 ppm iodine on a dry matter basis.[74] When fed either the 0.47 ppm iodine or 0.28 ppm iodine diet, 8 out of the 9 cats became euthyroid, while all 9 cats became euthyroid when fed the 0.17ppm iodine diet.[74] Subsequent studies showed that hyperthyroid cats fed diets with ≥ 0.39 ppm iodine did not maintain TT_4 concentrations within the reference interval, while cats fed diets with ≤ 0.32ppm iodine resulted in euthyroidism in 90% of hyperthyroid cats.[75,76]

In a study of client-owned hyperthyroid cats, feeding a controlled iodine diet (0.32ppm on a dry matter basis) decreased TT_4 concentration and improved clinical signs after consuming the diet for 4 weeks.[77] This study also found that 37% of the cats remained hyperthyroid 4 weeks posttreatment, and when reevaluated at 8 weeks posttreatment, 25% of cats remained hyperthyroid.[77] There were no adverse effects associated with feeding the iodine-controlled diet.[77] Although controlling dietary iodine appear to be safe, and result in a significant decline in TT4, there is concern that some cats remain hyperthyroid, and many cats do not achieve TT_4 concentrations in the lower half of the reference interval, indicating optimal control of hyperthyroidism may be difficult via diet modification alone.

Thyroidectomy

Thyroidectomy is a curative treatment option for feline hyperthyroidism, but the popularity of surgical treatment has declined over the past decade, in part due to the risk of

significant post-operative complications and because of the development and availability of non-surgical treatment options. Since over 70% of hyperthyroid cats have bilateral thyroid disease,[2] curative surgery requires bilateral thyroidectomy for most cats.[78] Multiple different surgical procedures have been described elsewhere.[78,79,80,81] Morbidity associated with surgical approaches results from disruption of important structures in proximity to the thyroid glands including the parathyroid glands, the carotid arteries, jugular veins, and recurrent laryngeal nerves. The most serious post-operative complication is severe hypocalcemia caused by iatrogenic damage to, or removal of, the parathyroid gland(s) during surgery.[78,79,80] Horner's syndrome, and laryngeal dysfunction, and/or laryngeal paralysis are other potential surgical complications.[78,79,80] Along with surgical complications specific to the thyroidectomy, geriatric hyperthyroid cats are often in poor body condition and may have concurrent disease(s), making them less desirable anesthetic candidates. In addition to surgical complications, treatment failures can also occur leading to persistent hyperthyroidism or permanent hypothyroidism. Persistent hyperthyroidism can result from incomplete thyroidectomy, or presence of unsuspected ectopic thyroid tissue, while cats that receive a complete bilateral thyroidectomy are at risk for permanent hypothyroidism.[78,79,80]

When evaluating the survival times of 101 cats that underwent either unilateral or bilateral thyroidectomy, 2 cats died within 72 hours of surgery.[3] Post surgical follow-up 59 months post-thyroidectomy revealed 57 cats were still alive with a median survival time of 1.9 years and 44 cats that were no longer alive and had a median survival time of 1.1 years.[3] Reported causes of death included renal failure, other malignant tumors, megacolon, aortic thrombosis, respiratory problems, seizures, urinary tract problems, viral infections, and liver disease. Ultimately, if thyroidectomy is chosen as the primary treatment for hyperthyroidism,

euthyroidism should be achieved prior to surgery via medical or dietary management. Euthyroidism at the time of surgery may diminish the risk for cardiac complications associated with anesthesia and permits assessment of renal function prior to thyroidectomy.

Radioiodine Therapy

Radioiodine (^{131}I) is another curative treatment for feline hyperthyroidism, and is the treatment of choice for most cats due to its high cure rate and minimal side effects. Because iodine transporters on thyroid cells do not differentiate ^{131}I from naturally occurring iodine, the radioactive isotope is able to concentrate within the thyroid gland. ^{131}I emits β-particles and γ-rays, which destroy any surrounding functional thyroid tissue.[55] β-particles cause the majority of the clinical effect by causing pyknosis and necrosis of thyroid follicular cells as well as vascular and stromal fibrosis of the gland.[55] The emitted radiation travels on average only 400μm within thyroid tissue and spares surrounding tissues such as the parathyroid glands.[55] In addition, atrophied thyroid tissue is unaffected by^{131}I due to its inability to uptake iodine, making ^{131}I the only treatment modality to specifically target hyperfunctioning thyroid tissue.[82]

^{131}I is typically administered by subcutaneous injection, although intravenous and oral administration is also acceptable.[37] Several methods for calculating an ^{131}I dose have been described.[53,55,83,84] Ultimately, treatment protocols that use variable ^{131}I doses (tailored to individual cats) have no advantage over protocols that employ a fixed ^{131}I dose, thus, most treatment centers report use of a fixed dose protocol that administers 3-6mCi per cat.[37,50,82,83] A study that evaluated 524 hyperthyroid cats treated with radioiodine used a single dose of 2-6mCi ^{131}I.[37] The administered dose was determined using a combination of severity of clinical signs, magnitude of serum T_4 elevation and size of the thyroid gland(s) measured via digital palpation.[37]

The investigators reported that there was complete resolution of clinical signs of hyperthyroidism and return of serum total T_4 concentration to within the reference interval in 94.2% of cases within 6-12 months of radioiodine therapy; only 8 cats remained hyperthyroid and 11 developed clinical hypothyroidism 12 months after ^{131}I treatment.[37] Based on these results, it is recommended that cats that remain hyperthyroid after an initial ^{131}I treatment should not undergo a second treatment until persistent hyperthyroidism has been documented at least 6 months post therapy.[37]

^{131}I doses of 10-30 mCi carries the best chance of completely destroying malignant thyroid tissue, making it the treatment of choice in cats with confirmed thyroid carcinoma, regardless of tumor location, including pulmonary metastases.[53,85] Larger doses of ^{131}I are needed for carcinomas because malignant thyroid cells do not concentrate or retain ^{131}I as effectively as adenomatous cells.[51,53,85] The use of high dose radioiodine in cats after thyroidectomy for carcinoma has been associated with a high rate of post-treatment hypothyroidism, requiring thyroxine supplementation.[85] However, another study that evaluated a single high-dose of ^{131}I as the sole therapy, found that 6 out of 7 cats with confirmed thyroid carcinoma had complete clinical resolution of hyperthyroidism and none of the cats had clinically significant hypothyroidism requiring supplementation post-^{131}I treatment.[51]

Potential disadvantages to ^{131}I therapy include persistent hyperthyroidism requiring a second ^{131}I treatment or use of anti-thyroid medication, as well as post-^{131}I hypothyroidism.[37,82] Of 524 cats treated with a mean radioiodine dose of 3.4 mCi, the percentage of cats with relapse of hyperthyroidism was only 2.5% and the prevalence of clinical hypothyroidism requiring thyroid supplementation was only 2.1%.[37] Additional disadvantages of radioiodine therapy include the need for patients to be housed separately for 7-10 days after treatment or until

radioactivity falls to safe levels as determined by state regulations. After discharge from the hospital, many cats will continue to emit low doses of radiation for approximately 2 weeks, which necessitates additional precautions be implemented to avoid unnecessary exposure of pet owners. In addition to specific in-hospital housing requirements, staff with radiation safety training are needed to care for the cats in the post-treatment period. Due to these factors, there is a relatively high upfront (but one time) cost for ^{131}I therapy.

In general, ^{131}I is a highly efficacious treatment modality, with 95% of cats becoming euthyroid within 3 months of receiving a single treatment.[55] The median survival times associated with ^{131}I therapy have been found comparable to or longer than those reported for cats that undergo surgical thyroidectomy.[3] The median survival time of the above-mentioned 524 cats that received ^{131}I was approximately 2 years.[37] Other reported median survival times of cats that received ^{131}I for treatment of treatment of hyperthyroidism are 25 months,[86] and four years.[68] Overall due to the low rate of short and long-term effects of radioiodine therapy, as well as comparable to increased survival times as compared to thyroidectomy, ^{131}I remains the curative treatment of choice for feline hyperthyroidism.

Conclusions

Hyperthyroidism is the most commonly diagnosed endocrinopathy in older cats, and its recognition and diagnosis are important to small animal practitioners. The pro's and con's of the available treatment options as well as long-term monitoring requirements should be discussed in detail with cat owners to ensure the most appropriate treatment plan is initiated for each individual cat. The costs associated with each treatment option vary based on the facility, and the relatively larger upfront cost of thyroidectomy and ^{131}I must be compared to the monthly

costs associated with the non-curative, lifelong treatment options. Due to the lack of a randomized trial evaluating all the different treatment options, it is difficult to state the superiority of one treatment modality over the other, emphasizing the need to tailor therapy to each individual cat and owner needs.

Chapter 2 - A Review of the Renal Effects of Feline Hyperthyroidism

Introduction to Feline Chronic Kidney Disease

Hyperthyroidism and chronic kidney disease (CKD) are both common diseases in the geriatric feline population and the frequency of concurrent hyperthyroidism and CKD in cats increases with age.[68,87] CKD is estimated to affect 1-3% of all cats,[88] and over 30% of cats older than 15 years of age.[89] Nephron damage associated with CKD is usually considered irreversible, and is often progressive. Most feline CKD is associated with tubulointerstitial lesions, although a primary etiology is often not determined. Renal diseases that have been linked with the development of CKD include glomerulopathies, pyelonephritis, nephrolithiasis, polycystic kidney disease, amyloidosis, and neoplasia. In some cases, the initial underlying renal insult remains undetected or untreated which allows continued damage to nephrons. It is also possible that when the initial insult is not resolved, progressive kidney damage becomes "self-perpetuating". CKD can progress over a period of months or years and is a leading cause of death in cats. To better classify CKD, the International Renal Interest Society (IRIS) has recommended a staging system that utilizes serum creatinine (SCr) concentration, proteinuria, and systolic blood pressure to help guide appropriate therapy as well as prognosis.[88] The median survival time of cats with CKD varies according to the IRIS stage of disease, with more advanced stages having decreased survival. A subset of CKD cats within the IRIS Stage 2 group (SCr concentrations between 2.3 mg/dl [203 μmol/l] and 2.8 mg/dl [250 μmol/l]) had a median survival time of 1,151 days, while cats with IRIS CKD Stages 3 (SCr concentrations between 2.9 mg/dl [251 μmol/l] and 5.0 mg/dl [440 μmol/l]) or stage 4 (SCr concentrations >5.0 mg/dl [>440 μmol/l]) had a median survival time of 679 and 35 days, respectively.[90] It is usually not

possible to improve renal function in CKD, as irreversibly damaged nephrons are replaced by fibrous scar tissue, and therefore treatment is lifelong and aimed at stabilizing renal function. The reported median survival time for cats with hyperthyroidism ranges from 1.6 years to up to 4 years,[20,37,68,86] while cats classified as having CKD prior to treatment of hyperthyroidism have shorter survival times of 0.5 years to up to 2 years.[20,68]

Effects Of Thyrotoxicosis On The Kidney

Thyrotoxicosis leads to hemodynamic changes throughout the body, many of which specifically affect the kidneys. One example is increased activation of the renin-angiotensin-aldosterone system (RAAS) which has been shown in both people and cats with naturally occurring hyperthyroidism.[91,92] Increased RAAS activation is not only due to T_3 having a direct effect on renin gene expression, but also T_3 mediated relaxation of vascular smooth muscle cells causing decreased peripheral vascular resistance by as much as 50%.[91,93,94,95] Secondary to the decrease in systemic vascular resistance, the effective arterial filling volume decreases and the RAAS is upregulated in an effort to restore effective arterial filling volume via increased renal sodium reabsorption within the proximal tubule and loop of Henle.[91,93] In addition, hyperthyroidism is associated with increased responsiveness and upregulation of β-adrenergic receptors within cardiac tissue as well as the renal cortex,[96] that can lead to increased sympathetic nervous system activity and increased RAAS activity.[91] Increases in RAAS activation leads to an overall increase in angiotensin II which is a potent vasoconstrictor of the glomerular efferent arteriole leading to increased glomerular pressure and glomerular hyperfiltration.

The other major effect of hyperthyroidism on the kidneys is an overall increase in glomerular filtration rate (GFR). This occurs secondary to hyperthyroid-associated decreased

vascular resistance, combined with increased cardiac output, and overall increased blood volume, causing increased renal blood flow (RBF), increased glomerular capillary hydrostatic pressure, and increased GFR. Additionally, GFR upregulation is enhanced secondary to thyroid hormone-induced increases in expression of mRNAs encoding for chloride channels, leading to increased chloride absorption in the proximal tubule and loop of Henle.[97] The decreased intratubular chloride load is sensed in the distal tubule by the macula densa and via tubuloglomerular feedback, GFR is further upregulated.

Renal proteinuria is a common finding in cats with hyperthyroidism as well as cats with CKD.[20,30] Increases in proteinuria associated with CKD have been hypothesized to occur secondary to increased glomerular capillary pressure and impaired tubular resorptive capacity of remaining nephrons.[98,99] Although the mechanism of proteinuria in hyperthyroidism is incompletely understood, clinically significant systemic hypertension due to hyperthyroidism is less common than initially thought,[20,100] thus the transmission of systemic hypertension to the glomeruli, may not be an important cause of proteinuria in hyperthyroid cats. Proteinuria is a risk factor for the development of azotemia,[101] and the progression of azotemic CKD.[102] Fortunately, the magnitude of proteinuria tends to decrease once the euthyroid state is restored.[20,103]

The presence or absence of azotemia (assessed via serum creatinine and serum BUN concentrations) and measurement of GFR are commonly used to evaluate renal excretory function in cats. The hypermetabolic state that accompanies hyperthyroidism leading to increased RBF and increased GFR, however, may affect the ability to interpret these parameters. Decreased creatinine production due to a reduction in muscle mass, as well as the aforementioned increases in GFR in hyperthyroid cats can make pre-treatment assessment of

renal excretory function using only the serum creatinine concentrations difficult, and can 'mask' existing kidney disease. In addition, the gold standard for assessment of renal excretory function is GFR measurement, however, the hyperthyroid-induced increases in RBF and GFR can make renal function appear normal despite the presence of CKD. These masking effects may result in the diagnosis of CKD being made only after euthyroidism is restored. The overall prevalence of concurrent azotemia and hyperthyroidism prior to hyperthyroid therapy in cats has been reported to range from 10%-23%,[13,20,68] while post-treatment azotemia occurs in approximately 15-49% of hyperthyroid cats.[20,65,68]

Effects Of Hyperthyroidism Treatment On Kidney Function

Regardless of the modality utilized, successful treatment of hyperthyroidism decreases renal excretory function, resulting in an increase in the serum creatinine concentration and a decrease in the GFR.[30,63,64,65,86,104,105] For example, in a study of 22 cats treated with ^{131}I, there was a significant decrease in GFR observed between day 6 and day 30 post-^{131}I treatment, and cats with normal renal excretory function prior to therapy had significant increases in serum creatinine and BUN concentrations within 30 days following treatment.[104] When evaluating the long-term renal effects of ^{131}I in 27 cats, serum creatinine concentration increased significantly at 1-month post treatment and continued to increase at 3 and 6 months post-^{131}I.[65] Conversely, GFR decreased significantly at 1 month after treatment, and continued to decrease 6 months after treatment, although the decrease beyond 1 month was not significant.[65] Similar results were observed in another study,[30] in which GFR decreased significantly until four weeks post-^{131}I treatment and then stabilized.[30] Additionally, in 268 non-azotemic hyperthyroid cats treated with either antithyroid medication alone, or antithyroid medication in combination with

thyroidectomy, 15% became azotemic by 8 months post-treatment.[20] Importantly, it has been shown that cats that develop post-treatment azotemia do not have decreased survival times compared with hyperthyroid-treated cats that remain nonazotemic.[106] However, cats with azotemia prior to initiation of treatment for hyperthyroidism appear to have decreased survival compared with cats that become azotemic following treatment.[20-68] Collectively, these studies indicate that serum creatinine concentration may continue to increase for 6 months after attaining a euthyroid state, while GFR decreases for up to 1 month, and then tends to stabilize.

Effects Of Hypothyroidism On The Kidney

Hypothyroidism has been associated with decreased GFR in dogs,[107] and similar physiology is suspected in cats. Diminished GFR could have significant consequences for hyperthyroid cats with preexisting renal disease that become hypothyroid as a result of treatment. In 80 hyperthyroid cats treated either with anti-thyroid medication alone or in combination with thyroidectomy, 28 cats were diagnosed with hypothyroidism 6 months post therapy based on decreased total T4 concentration and increased TSH concentration.[106] Of these 28 hypothyroid cats, 16 (57%) developed post-treatment azotemia which not only was higher than the proportion of euthyroid cats that developed post-treatment azotemia (30%), but was associated with a significantly shorter survival time than the nonazotemic hypothyroid cats.[106] Thus, cats with iatrogenic hypothyroidism are not only more likely to develop azotemia, but hypothyroid cats with azotemia also have decreased survival.[106] When decreasing the dose of anti-thyroid medication in hyperthyroid cats that became hypothyroid following medical treatment with anti-thyroid medication, resolution of azotemia occurred in 50% of cats.[108] Based on these findings, the importance of identifying and treating cats with iatrogenic hypothyroidism becomes

apparent. Hypothyroidism may not occur for as long as 3-6 months after radioiodine treatment,[106] so monitoring TT_4 for at least 6 months post-treatment is necessary. A low total T_4 concentration alone is not sufficient for diagnosis of iatrogenic hypothyroidism due to the potential for euthyroid sick syndrome.[109] The combination of reduced total T_4 concentration and elevated TSH concentration is consistent with iatrogenic hypothyroidism. In this circumstance, thyroxine supplementation or adjustment of antithyroid medication should be considered.[109]

Pretreatment Predictors Of Posttreatment Azotemia

Although the prognosis for cats that develop post-treatment azotemia is similar to hyperthyroid-treated cats that remain nonazotemic,[106] the ability to predict which cats will experience decreased renal function post-hyperthyroidism therapy has been widely sought after. To date, pretreatment values for serum creatinine, serum BUN, and USG have not been shown to reliably predict development of azotemia after treatment of hyperthyroidism.[13,64,65,66,86,87] In one large study, plasma concentration of urea and creatinine were positively correlated and plasma globulin concentration was negatively correlated with the development of post-treatment azotemia,[20] however other studies have not confirmed these results. Pre-treatment measurement of GFR has shown promise for predicting post-treatment azotemia in some studies,[104] however other studies have shown significant overlap in GFR values.[30] For these reasons, novel markers of tubular damage have been investigated for predicting development of azotemia after treatment for hyperthyroidism.

Many untreated hyperthyroid cats exhibit mild proteinuria, which when evaluated by urine protein to urine creatinine ratio (UPC), has been shown to significantly decrease 4 weeks after successful treatment of hyperthyroidism.[20,30] In contrast to the UPC, one study

demonstrated that the urine albumin to creatinine ratio (UAC) did not decrease with successful treatment of hyperthyroidism suggesting that albuminuria may not be a major contributor to the proteinuria observed in hyperthyroid cats.[20] Although resolution of proteinuria (as measured by UPC) after treatment of hyperthyroidism is an important finding, the use of pretreatment UPC values as a predictor of post-treatment azotemia was not supported.[20,30]

N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal glycosidase enzyme found primarily in the epithelial cells of the proximal convoluted tubule. Increased concentration of this enzyme in the urine is considered a specific marker of active proximal tubular damage.[110] Urine NAG activity is typically expressed in a ratio with urine creatinine, referred to as NAG index (U/g) (NAG_i). In 24 hyperthyroid cats treated with methimazole, the pre-treatment NAG_i did not differentiate azotemic euthyroid cats from nonazotemic euthyroid cats after treatment.[67] However, the NAG_i measured in untreated hyperthyroid cats decreased following therapy, indicating the renal tubule changes associated with hyperthyroidism can be reversed following return to euthyroidism.[67]

Urinary retinol binding protein (uRBP) is a sensitive indicator of renal tubular damage in people, with minor tubular dysfunction leading to increased urinary excretion of uRBP.[111] When comparing uRBP levels (expressed as uRBP:urine creatinine ratio) between clinically healthy cats, cats with CKD, and cats with hyperthyroidism, the CKD and hyperthyroid groups had elevated uRBP, while uRBP in the healthy cats was below the assay sensitivity.[112] In 10 cats with naturally occurring hyperthyroidism evaluated pre- and post-^{131}I treatment, a significant decrease in the uRBP:urine creatinine ratio was detected following successful treatment.[113] This data suggests that return to a euthyroid state can reverse some of the tubular changes that result

in increased uRBP in the hyperthyroid state, however uRBP has not been shown to be predictive of post-treatment azotemia.[113]

As previously discussed, there is increased activation of the RAAS in hyperthyroid cats.[91,92] The subsequent elevations in angiotensin-II, which preferentially constricts the efferent glomerular arteriole, may lead to decreased peri-tubular blood flow and peri-tubular hypoxia. Vascular endothelial growth factor (VEGF) is a regulator of blood vessel growth, and in people is produced by renal proximal tubular cells in response to hypoxia *in vitro*.[114] Inasmuch as urinary vascular endothelial growth factor:creatinine ratio (VEGFCR) may be a marker for renal tubular hypoxia, its potential association with the development of azotemia in hyperthyroid cats following treatment has been investigated.[115] VEGF excretion was positively associated with both hyperthyroidism and RAAS activation, and VEGF excretion decreased following treatment of hyperthyroidism. However, this study also revealed that VEGFCR was not correlated with the development of azotemic chronic kidney disease post-treatment, and thus, tubular hypoxia may not be a mechanism for renal damage in hyperthyroid cats.[115]

Conclusions

To date, no single, readily available, serum or urinary biomarker is able to reliably predict post-treatment renal function in hyperthyroid cats.[13,20,64,65,66,86,87] Although successful treatment of hyperthyroidism has the potential to unmask pre-existing CKD, the associated changes in renal function are usually mild, renal function typically stabilizes within 6 months of the hyperthyroid treatment, and overall survival of those cats that do become azotemic does not differ from non-azotemic cats. Thus, treatment of hyperthyroidism is recommended with the target total T4 in the lower half of the reference interval, without creating hypothyroidism. When treating non-azotemic hyperthyroid cats, it is important to remember that increases in

serum creatinine concentrations may occur over several months, so monitoring renal function for 6 months following restoration of euthyroidism is recommended. When treating cats with evidence of CKD prior to treatment, the decreased survival times associated with pre-therapy CKD should be discussed with owners, and continued monitoring of renal function for months following return euthyroidism is necessary. In addition, due to the increased risk of azotemia and poor prognosis in cats with iatrogenic hypothyroidism, total T4 (and TSH when appropriate) concentrations should be monitored for at least 6 months after euthyroidism is achieved, and iatrogenic hypothyroidism should be corrected via adjustment of anti-thyroid medication or thyroid supplementation when necessary.

Chapter 3 - Assessment of Renal Function in Hyperthyroid Cats Managed with a Controlled Iodine Diet.

Introduction

Since its recognition in the late 1970's,[1] hyperthyroidism has become the most commonly diagnosed endocrinopathy in older cats. Treatment modalities have classically included antithyroid medication (methimazole or carbimazole), thyroidectomy, and radioiodine (^{131}I) therapy. Previous studies have demonstrated that glomerular filtration rate (GFR) significantly declines following treatment of hyperthyroidism independent of the treatment modality used.[63,64,65,104] Recently, Hill's® Prescription Diet® y/d® Feline, a controlled iodine food, has been introduced as a reversible treatment option for management of feline hyperthyroidism.[74,75] In client-owned hyperthyroid cats, feeding y/d® Feline lead to a significant decline in total T_4 concentrations and resolution of clinical signs of hyperthyroidism within 4 weeks without adverse effects.[77] In contrast to other treatment modalities, the serum creatinine concentration in cats fed the iodine-controlled diet, significantly decreased ($p = 0.001$) after four weeks of therapy. Additional effects of Hill's y/d® on renal function in hyperthyroid cats have not been evaluated.

GFR measurement is considered the gold standard for evaluation of renal excretory function, however due to increased time, labor and expense, plasma clearance techniques that approximate GFR are not routinely performed in clinical practice. Measurement of serum creatinine concentration is the most commonly assessed renal excretory function parameter, however, the loss of muscle mass in hyperthyroid cats can decrease production of creatinine and decrease its serum concentration. Serum symmetric dimethyl arginine (SDMA) is a byproduct of

protein methylation that is largely excreted by the kidneys.[116] In people, serum SDMA is an endogenous marker of renal function, has been shown to correlate with GFR, and appears to be a more sensitive biomarker than serum creatinine for assessing renal dysfunction.[117] Recently the reciprocal of serum SDMA was found to be linearly related to GFR in cats with chronic kidney disease (CKD).[118] In addition, there is evidence that serum SDMA is a sensitive biomarker for CKD in cats; allowing earlier detection of CKD compared with serum creatinine concentration.[119]

The first aim of this study was to evaluate the effects of y/d® Feline on renal function in client-owned cats with natural occurring hyperthyroidism after 6 months of treatment. Renal function was assessed by plasma clearance of ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), and serum creatinine and SDMA concentrations. The second aim was to evaluate the effects of the controlled-iodine food on overall muscle mass via ultrasonographic evaluation of the epaxial muscle diameter (EMD). It was hypothesized that controlled dietary iodine as a treatment for hyperthyroidism would create a euthyroid state without a decrease in renal function. In addition, it was hypothesized that feeding y/d® Feline to hyperthyroid cats would not decrease muscle mass.

Materials and Methods

Animals

Cats were recruited from the Kansas State University Veterinary Health Center (KSU-VHC) patient population and from surrounding primary care veterinary hospitals. The Institutional Animal Care and Use Committee of Kansas State University approved the study and written owner consent was obtained prior to patient entry into the study.

Inclusion Criteria

Newly diagnosed, or previously diagnosed hyperthyroid cats on anti-thyroid medication were eligible for inclusion in the study. Any anti-thyroid medication was discontinued for at least one week prior to evaluation at KSU-VHC. Hyperthyroidism was confirmed via elevated chemiluminescent enzyme immunoassay (CLEIA) total thyroxine (T_4) [TT_4] concentration[a], a Michigan State University (MSU) thyroid function panel (TT_4, TT_3, fT_4ED, fT_3, and TSH)[b] and thyroid technetium scan.

Exclusion Criteria

Cats were excluded from the study if they had previous ^{131}I treatment for hyperthyroidism, or evidence of significant comorbidities such as diabetes mellitus, neoplasia, and chronic kidney disease. In addition, if the patient had a fractious temperament that did not allow frequent handling or multiple sample collections, they were excluded. Finally cats were excluded if they refused to reliably eat the diet, or if the owners were unable to ensure that y/d® Feline was the only source of nutrition throughout the study period.

Study Design

A 6-month, prospective, observational study was conducted. Cats that fulfilled the inclusion criteria were transitioned to Hill's y/d® Feline either dry or canned formulations, based on cat/owner preference, as the sole source of nutrition over the course of one week. Owners were provided instructions detailing diet transition guidelines with the goal of meeting the cats resting energy requirements (RER) with y/d® Feline by the end of the one week period. RER was calculated for each cat using the equation of 1.4[(30 x body weight (kg) + 70] and the amount of dry and/or canned food required to meet these requirements was discussed with the owners. In addition, food storage information was provided to help ensure no cross-

contamination with other foods or products that could potentially contain iodine. Each cat was re-evaluated after consuming the controlled-iodine diet exclusively for 1 month, 2 months, 3 months and 6 months. The cats' willingness to eat the food, and owners' ability to maintain strict dietary compliance was discussed at each visit.

Initial Hospital Visit

Initial evaluation to confirm the diagnosis of hyperthyroidism and to rule out comorbidities included physical examination, body weight, CLEIA TT_4 concentration[a], MSU thyroid function panel[b], complete blood count (CBC), serum biochemistry, serum SDMA[c], urinalysis, aerobic bacterial urine culture, urine protein to creatinine ratio (UPC), urine gamma-glutamyl transpeptidase (GGT) to creatinine ratio (UGGTC), semi-quantitative feline specific albuminuria assay (ERD)[d], Doppler[e]-measured systolic blood pressure (SBP), thyroid technetium scan, plasma clearance of ^{99m}Tc-DTPA, and ultrasound assessment of EMD and thyroid gland volume.

Subsequent Hospital Visits

A follow-up evaluation was scheduled when the cat had been exclusively eating y/d® Feline for 1 month, 2 months, 3 months and 6 months. Evaluation at 1 and 3 months included physical examination, body weight, CLEIA TT_4 concentration[a], CBC, serum biochemistry, serum SDMA[c], urinalysis, UPC, UGGTC, ERD[d], and SBP[e]. The 2-month evaluation included only CLEIA TT_4 concentration to help document continued dietary compliance, and the final 6-month evaluation included all diagnostics performed at 1 and 3 months in addition to repeating the MSU thyroid panel, ^{99m}Tc-DTPA plasma clearance and ultrasonographic assessment of EMD and thyroid gland volume. All ultrasonographic assessments of the epaxial muscles and thyroid glands and were performed by the same board certified radiologist.

Blood and Urine Sample Collection and Analysis

Blood samples were collected from the jugular or medial saphenous vein. All urine samples were collected by cystocentesis. Serum was stored at -80°C from each recheck evaluation and SDMA concentrations measured as previously described.[119] Urinalysis was performed using a refractometer for USG, commercially available reagent strips[f] for chemical evaluation, and standard microscopic sediment examination. Approximately 2 mL of urine were set aside for the ERD, which was performed within an hour of collection and interpreted as either negative, low positive, medium positive or high positive. For statistical analysis, the results of the ERD were scored as follows; negative = 0, low positive = 1, medium positive = 2, high positive = 3. Approximately 0.5 mL of urine was saved from each urine sample and refrigerated until submitted, within 2 hours, for aerobic culture and sensitivity (initial evaluation and as indicated by urine sediment evaluation on subsequent evaluations). Urine protein was quantified using the benzethonium reaction method and urine creatinine was quantified using the buffered Jaffe reaction, both with an automated chemistry analyzer[g]. The UPC was calculated from this data for each urine sample. Urine GGT was quantified using the enzymatic colorimetric assay, and the UGGTC was then calculated using the same urine creatinine value for the UPC calculation.

Blood Pressure Measurement

Systolic blood pressure measurements were obtained by use of an ultrasonic Doppler[e] monitor after the cats were acclimated to the hospital environment. Cats were placed in lateral recumbency. The up forelimb was used for pressure measurement with a neonatal #2 or #3 cuff (width approximately 35-40% the circumference of the leg) placed below the elbow. After clipping directly over the common digital branch of the radial artery, 3-4 readings were obtained

and the mean was recorded. Cats that had persistent hypertension (systolic blood pressure >180mmHg on ≥ 2 measurements at least 1 week apart) were started on once daily oral amlodipine[h] at 0.625mg per cat, with the dosage adjusted as needed upon reevaluation.

Imaging

The same board-certified veterinary radiologist performed all ultrasonographic evaluations of the left and right epaxial muscles and thyroid glands. When required, ketamine (5mg/kg, IV) and diazepam (0.5mg/kg, IV) were administered for sedation. For the EMD, three measurements were taken and the mean recorded. For the thyroid gland, three measurements of each of the following; gland length, width and height, were taken and the mean recorded, the volume was then calculated by multiplying the mean length, width and height to give a measure of mm^3. Thyroid scintigraphy was performed as previous described.[47] The thyroid to zygomatic salivary gland ratio was calculated for both thyroid glands, and a ratio > 1.2:1 was considered consistent with hyperthyroidism.[48] Unilateral disease was defined as one thyroid gland with a thyroid to salivary gland ratio >1.2:1 and bilateral disease was defined as both thyroid glands with a thyroid to salivary gland ratio >1.2:1.

Determination of GFR

Glomerular filtration rate was determined by analysis of a ^{99m}Tc-DTPA plasma disappearance curve. Baseline plasma clearance studies were performed on the second day of initial evaluation, after results of screening blood and urine tests had been obtained. Doses of ^{99m}Tc-DTPA for injection and for a standard were drawn and measured in milicuries (mCi) by use of a dose calibrator. The standard was prepared by placing approximately 1 mCi of ^{99m}Tc-DTPA in a volumetric flask and adding water to make a total volume of 1 L. Approximately 1 mCi of ^{99m}Tc-DTPA was administered via the cephalic vein. Pre- and post injection syringe

activity was counted, using a scintillation probe, to determine the exact dose of radioisotope administered. Time zero was recorded. Blood samples were collected via jugular vein, or the medial saphenous vessel opposite the injection site at 15, and 120 minutes. Plasma was harvested from centrifuged blood anticoagulated with ethylenediaminetetraacetic acid (EDTA). One-milliliter aliquots of the diluted standard and plasma samples were prepared for each sample collection time. A single-channel analyzer system attached to sodium iodide well crystal was used to determine radioactivity in each sample. The GFR was calculated from ^{99m}Tc-DTPA plasma disappearance curves as previously described.[120]

Statistical Analysis

Analyses were performed using commercial software[i]. Descriptive statistics were presented as mean ± standard deviation (SD). Serum creatinine concentration, GFR, and serum SDMA were compared using repeated measures ANOVA to analyze the difference between pre and post treatment effects. T-tests were used for evaluation of change over time. Significance was set at $p \leq 0.05$.

Results

A total of 18 cats were evaluated as possible participants in the study, of which 15 met all of the inclusion criteria. Of the three cats excluded, one cat was excluded due to refusal to eat the food, and another after the owner was unable to ensure strict dietary compliance. The third cat was removed from the study two weeks after the 2-month recheck due to a decreasing appetite, despite tempting with food other than y/d® Feline, and worsening lethargy. Upon evaluation, the cat was clinically icteric, with moderate liver enzyme elevations and a diffusely hyperechoic liver with rounded margins on abdominal ultrasound. The cat was admitted to the hospital and treatment of presumptive hepatic lipidosis was instituted with IV fluid therapy,

vitamin K administration SQ, SAMe, and ursodiol. An esophageal feeding tube was placed on day two and tube feedings were increased to total RER over 3 days. Unfortunately, the cat had minimal response after 6 days of therapy, and the owner requested euthanasia. Necropsy evaluation revealed diffuse, moderate to severe hepatic lipidosis, diffuse, severe pancreatic amyloidosis with interstitial fibrosis, and unilateral thyroid adenoma.

The age of cats included in the study ranged from 7-16 years old with a median of 12 years of age. Of the fifteen cats, 13 were spayed females and 2 were castrated males. Majority of cats were domestic short hairs (n=13), and there was one each of the following; domestic long hair, Maine Coon cat, and Siamese cross. All cats had an initial TT_4 concentration >56 nmol/L (reference interval 10-45 nmol/L) via CLEIA (Table 3.1) and > 49 nmol/L (reference interval 10-55 nmol/L) via MSU. Results of the technetium thyroid scan (Table 3.2) revealed all cats had at least one thyroid to zygomatic salivary gland ratio of >1.2, consistent with hyperthyroidism. Two of the cats had unilateral disease, while 13 had bilateral disease, and no cats had ectopic thyroid tissue.

The mean body weight (kg), USG, UGGTC, ERD, SBP, EMD (left and right [cm]) and thyroid gland volume (mm^3) at each available evaluation are listed in Table 3.3. There was no difference found between any of these parameters throughout the study period. Based on persistent hypertension on repeat blood pressure measurements, cats 1, 3, 4 and 15 were treated with amlodipine (average dose of 0.66 mg by mouth once daily). Results of the MSU thyroid panel for each of the 15 cats pre and posttreatment are listed in Table 3.4, and the mean values for CLEIA TT_4, GFR, SCr, SDMA and UPC pre and posttreatment are listed in Table 3.5.

The mean serum CLEIA TT_4 concentration significantly decreased ($p < 0.001$) from a pretreatment value of 185.54 ± 138.0 nmol/L to a 6-month posttreatment value of 60.5 ± 35.5

nmol/L (reference interval 10-45 nmol/L) (Table 3.5). These values were similar to the mean MSU thyroid panel results of 106.9 nmol/L for the pretreatment value and 57 nmol/L 6-months posttreatment. There was no significant difference in TT_4 (CLEIA or MSU) between baseline and 6-months posttreatment. Of the 15 cats that completed the study, 5 cats were euthyroid (CLEIA TT_4 concentration within reference interval) at the end of the 6-month study period, while the remaining 10 cats had TT_4 concentrations above the reference interval (Table 3.1). Based on the MSU thyroid panel results, 6/15 cats were euthyroid and 10/15 had a $TT_4 \leq 60$ nmol/L (Table 3.4).

There was a significant decrease in serum creatinine concentration between the initial evaluation and 6 months posttreatment ($p < 0.001$). No significant differences were observed between the initial and 6-month posttreatment GFR ($p = 0.71$), serum SDMA ($p = 0.41$), UPC ($p = 0.74$, or EMD ($p = 0.95$ and $p = 0.45$ for right and left EMD respectively) (Table 3.5).

Discussion

Similar to previous studies assessing the effects of y/d® Feline, the results of this study indicate that feeding y/d® Feline to hyperthyroid cats results in a significant decrease in circulating TT_4 concentration. Despite the significant decrease in TT_4, the circulating TT_4 concentration was still elevated above reference interval in 10/15 (66%) and 9/15 (60%) depending on the TT_4 assay, of the cats at the end of the 6-month study period. A potential cause for continued hyperthyroidism in these cats could be attributed to either poor patient or owner dietary compliance. Poor dietary compliance was documented in 24/68 cats fed y/d® Feline in a previous study,[77] however in the present study, no specific concerns about compliance were reported by owners at recheck evaluations. Because many households are not only multi-cat

house holds, but also inhabited by other pets, as well as children and intermittent visitors, accidental or unknown exposure to other dietary sources is difficult to completely rule-out.

In contrast to previous studies,[30,63,64,65] management of hyperthyroidism with y/d® Feline did not result in a decrease in GFR. The most likely explanation for the lack of significant decline in GFR in the present study was the relatively high TT_4 concentrations posttreatment. Previous studies assessing the effects of treatment on GFR, found TT_4 concentrations were within or below the reference interval in all cats at the end of the study period.[63,64,65,104] Since the mean 6-month posttreatment TT_4 for cats in the present study was greater than the reference interval, post-treatment GFR values for those cats that were euthyroid via CLEIA at 6-months (n = 5) were looked as separately from the cats that remained hyperthyroid (n = 10), and no change in GFR was observed in the euthyroid group ($p = 0.35$). In addition, when evaluating the change in TT_4 and GFR in previous studies,[63,64,65] there was a correlation ($r^2 = 0.53$, $p < 0.0001$) between the TT_4 and GFR in each of the studies, whereas no correlation between TT_4 and GFR was observed in the present study ($r^2 = 0.06$, $p = 0.39$).

The lack of decline in GFR could also be associated with the absence of TT_4 concentrations below the reference interval at any time point for any cat in this study. In previous studies,[30,63,64,65] the number of cats with TT_4 below the reference interval ranged between 25-79%. Without concurrent TSH concentrations, it is unknown whether these cats were hypothyroid or euthyroid sick. It has been previously shown that GFR is negatively affected by hypothyroidism in dogs,[107] and similar physiology is suspected in cats. Therefore, the potential contribution of hypothyroidism to the decline in GFR with other treatment modalities is unknown, however none of the cats in the present study had TT_4 concentrations below reference interval.

Another explanation for the lack of significant decline in GFR in the present study could be related to a more gradual decline in TT_4 when y/d® diet is used to manage hyperthyroidism compared with other treatment modalities. As already discussed, although there was a significant decline in TT_4 after 1-month of feeding y/d® Feline, 60-66% of our patient population remained hyperthyroid at the end of the 6-month period, with 9/15 (60%) remaining hyperthyroid via CLEIA at 1- and 2-months posttreatment, and 12/15 (80%) remaining hyperthyroid at 3-months posttreatment. In a previous study evaluation y/d® Feline in client owned cats,[77] 25% of the patients evaluated remained hyperthyroid at 8 weeks. The number of hyperthyroid cats remaining 2-months after institution of y/d® Feline, could simply be due to lack of owner or cat compliance, however, it is also possible that the overall decline in TT_4 occurs more gradually than modalities. In a study population of cats fed y/d® Feline, serum TT_4 concentrations normalized within 4 to 12 weeks of initiating nutritional management and 90% of hyperthyroid cats maintained with the limited-iodine food as the sole source of nutrition became euthyroid.[76] The slope of TT_4 decline in client-owned hyperthyroid cats fed y/d® Feline has not been evaluated prior to 1-month posttreatment, however it has been shown that ^{131}I causes a significantly decrease just one week post therapy,[30] with a corresponding significant decrease in GFR, and similar timing for significant declines in TT_4 would be expected for bilateral thyroidectomy. The lack of change in EMD throughout this study could also be an indirect indicator of a more gradual decline in TT_4, and thus more gradual change in overall body condition. Other studies[30,65] have sighted increasing muscle mass as a source of increased serum creatinine concentrations overtime based on improved body condition, which may be associated with a more acute reduction in TT_4 allowing body condition changes to be appreciated sooner.

Serum creatinine concentration decreased ($p < 0.001$) between initial evaluation and 6-months posttreatment. This is contrary to other treatment modalities,[30,63,65] but similar to another study evaluating the effects of y/d® Feline in client owned hyperthyroid cats.[77] A possible reason for the observed decrease in serum creatinine concentration may be the lower content of heat-processed meat in the y/d® Feline as compared to other commercial cat foods. Increased consumption of heat-processed meats has been shown to increase circulating creatinine concentrations in people,[122] presumably associated with increased creatinine absorption from the gastrointestinal tract. A decrease in muscle mass was postulated as a potential cause for the decrease in serum creatinine concentration in a previous study,[77] however the present study showed no change in EMD suggesting decreased muscle mass was less likely to be the cause for the decreased serum creatinine concentration.

The EMD of both the left and right epaxial muscles as determined by ultrasonographic measurement did not change over time in our study population. The evaluation of the epaxial muscles for the evaluation of overall muscle mass has been utilized when assessing methods for evaluating sarcopenia in old dogs.[121] In that study the ultrasonographic margins of the epaxial muscles were defined medially by the spinous process of T13, ventrally by the 13th rib and dorsally and laterally by subcutaneous fat and normalized for variable skeletal size by dividing epaxial muscle area by the height of the body of T13.[121] Ultrasonographic measurement was compared the CT and radiographic measurement of epaxial muscle height.[121] Epaxial muscle area was significantly lower in healthy old dogs than young dogs when muscle area was measured by ultrasonography or CT, especially when the measurements were normalized for vertebral body height, while radiographic measurement did not appear to provide sufficient precision.[121] It seems reasonable that the use of ultrasonographic measurement of the epaxial

muscles in cats would provide similar information regarding overall muscle mass, however this has not been specifically evaluated.

Similar to GFR, SDMA concentrations did not change at any study time point. Previous studies of serum SDMA in cats demonstrated a linear correlation between serum SDMA and GFR,[118] and the present study found a similar correlation. Indeed, compared to SCr, serum SDMA was more highly correlated with GFR ($r^2 = 0.50$ vs. 0.30, $p = 0.04$). Thus, serum SDMA may be a better marker for GFR than serum creatinine in hyperthyroid cats. Further study of serum SDMA in hyperthyroid cats is warranted.

There was no change in UPC, UGGTC or ERD observed throughout the study period. The lack of change in UPC is contrary to other reports,[20,30] in which there were significant decreases in UPC 4 weeks post ^{131}I treatment. This difference may be due to the low number of cats in our study that had significant pretreatment proteinuria, in comparison to the previously reported 85% of cats with pretreatment proteinuria.[30] Lack of decline in ERD is similar to a previous study that found the urine albumin to creatinine ratio (UAC) did not decrease following successful treatment of hyperthyroidism.[20] The lack of decline in ERD in the present study may suggest that albuminuria is not a major contributor to the proteinuria observed in hyperthyroid cats as described elsewhere,[20] but is more likely associated with our relatively low number of proteinuric cats.

A limitation of this study was the relatively small number of cats that were considered euthyroid at the end of the study period, effectively decreasing the sample size and making data interpretation more difficult. Every effort was taken to ensure that owners were adequately storing and administering the food, while ensuring the cats were not receiving any other source of nutrition, however 100% compliance was difficult to confirm. It is likely that

unrecognized non-compliance contributed to the high percentage of cats that remained hyperthyroid. Although there was no difference found in the change in GFR vs. change in TT_4 in these five-six euthyroid cats, confirmation of this finding is warranted with a larger sample of euthyroid cats prior to and following treatment with y/d® Feline.

Conclusions

Feeding y/d® Feline for 6-months resulted in a significant decline in TT_4 concentration without adverse effects. Compared with other treatment modalities for feline hyperthyroidism, feeding y/d® Feline did not result in a significant decline in GFR, did result in a significant decrease in SCr, and had no change in EMD. In addition, there is evidence that serum SDMA may be a better marker for GFR than SCr in hyperthyroid cats.

Tables

Table 3.1 TT_4 concentrations over time as measured by CLEIA

CLEIA TT_4 Concentrations (nmol/L) – Reference Interval 10-45 nmol/L					
Patient	Baseline	1-month	2-month	3-months	6-month
1	436	79.7	58.9	48.6	55
2	236	265	112	85.2	59
3	128	56.1	41.8	51.2	39.8
4	66.8	32.3	18.8	46.7	33.8
5	426	56.1	54.7	73	78.8
6	421	118	69.5	136	176
7	62.3	19.7	21.1	11	19.1
8	72.6	44.3	39.1	42.7	46.9
9	149	46.9	46.3	57.7	72.6
10	236	71.6	57	66.5	54.4
11	90.1	42.9	37.8	62.2	67.7
12	82	45.3	46	52.1	43.2
13	136	38.2	39.7	34.8	54
14	185	39.7	64.1	86.1	64.2
15	56.3	60	81.6	54.6	43
Mean	**185.54**	**67.72**	**52.56**	**60.56**	**60.5**

Table 3.2 Thyroid to zygomatic salivary gland ratios

	Thyroid to Zygomatic Salivary Gland Ratio	
Case No.	Right	Left
1	11:1	39.7:1
2	19.4:1	5.7:1
3	3.78:1	1.43:1
4	5.66:1	1.88:1
5	45.75:1	17.04:1
6	47.23:1	2.99:1
7	2.19:1	6.08:1
8	0.84:1	4.39:1
9	2.33:1	10.45:1
10	5.19:1	33.26:1
11	7.45:1	4.2:1
12	3.24:1	4.02:1
13	No uptake	13.12:1
14	3.05:1	7.65:1
15	3.91:1	3.42:1
Mean	**11.5:1**	**10.36:1**

Table 3.3 Variables evaluated before, 1, 3, and 6-months after treatment: body weight, USG, UGGTC, ERD, SBP, EMD and total thyroid volume

	Initial	1-Month	3-Month	6-Month
Body weight (kg)	4.13 (2.78-7.4)	4.21 (2.83-7.12)	4.23 (3.00-7.17)	4.10 (2.97-6.76)
USG	1.025 (1.012-1.051)	1.027 (1.011-1.061)	1.022 (1.008-1.061)	1.024 (1.012-1.057)
UGGTC	0.43 (0.2-1.3)	0.29 (0.1-0.5)	0.34 (0.1-0.8)	0.30 (0.1-0.9)
ERD	1 (0-2)	0.8 (0-2)	0.93 (0-2)	0.67 (0-2)
SBP (mmHg)	156 (125-190)	155 (115-200)	154 (120-190)	156 (120-195)
Right EMD (cm)*	1.55 (1.2-2.03)	n/a	n/a	1.56 (1.07-2.15)
Left EMD (cm)*	1.56 (1.2-2.01)	n/a	n/a	1.62 (1.05-2.09)
Total Thyroid Volume (mm^3)*	369	n/a	n/a	281

Data are listed as mean and (range) values.
The ERD values were scored as follows; negative = 0, low positive = 1, medium positive = 2, high positive = 3
***Not all cats had all measurements available for EMD or thyroid gland volume calculations, the existing data was used in the analysis**

Table 3.4 Michigan State University (MSU) thyroid function panel results

	TT_4 (nmol/L)		TT_3 (nmol/L)		fT_4ED (pmol/L)		fT_3 (pmol/L)		TSH (mU/L)	
Case No.	Initial	6 Month	Initial	6 Month	Initial	6 Month	Initial	6 Month	Initial	6 Month
1	>156	54	4.1	2.6	>128	35	10.8	5.7	0	8
2	>156	59	>4.7	1.8	>128	46	9.6	5	0	0
3	95	48	1.4	1.1	105	46	4.2	2.1	9	0
4	73	40	1.5	1.4	53	43	2.4	2	0	0
5	>156	68	4	1.9	>128	60	9.6	2.4	0	0
6	>156	125	3.7	2.9	>128	>128	17.4	5	9	0
7	79	18	0.9	0.4	69	27	1.2	1	8	0
8	50	47	1.1	0.8	64	35	2.3	1.8	0	0
9	101	63	2.5	2	104	55	6.8	4.3	0	0
10	>156	56	3.1	2.2	>128	59	8.4	4.8	0	0
11	77	59	0.9	0.8	73	49	1.8	2.2	0	0
12	64	33	1	0.7	74	44	3.1	1.2	0	0
13	96	60	2	1.4	>128	63	2.6	3.2	0	7
14	116	79	1.6	1.9	110	57	2.7	5.4	0	0
15	67	58	1.1	1.3	42	45	3.3	2.7	0	0
Mean*	**106.9**	**57.8**	**2.25**	**1.55**	**97.87**	**52.87**	**5.75**	**3.25**	**1.73**	**1**

Reference intervals: TT_4 = 10-55 nmol/L, TT_3 = 0.6-1.4 nmol/L, fT_4ED = 10-50 pmol/L, fT_3 = 1.5-6.0 pmol/L, TSH = 0-21mU/L.

***For mean calculations: TT_4 values >156, a value of 157 was used, TT_3 values >4.7, a value of 4.8 was used, and fT_4ED values >128, a value of 129 was used.**

Table 3.5 Variables evaluated before and 6-months after treatment: CLEIA TT_4 concentration, GFR, SCr concentration, and serum SDMA concentration

	TT_4 (nmol/L)		GFR (ml/min/kg)		SCr (mg/dl)		SDMA (µg/dl)		UPC	
Case No.	Initial	6 Months	Initial	6 Months	Initial	6 Months	Initial	6 Months	Initial	6 Months
1	436	55	3.14	3.27	1.4	1.4	27	25	0.4	0.5
2	236	59	1.62	1.72	0.6	0.9	10	10	1.3	0.3
3	128	39.8	1.7	2.18	1.9	1.5	23	19	0.5	0.5
4	66.8	33.8	3.03	2	1.1	0.8	8	8	0.3	0.5
5	426	78.8	2.45	2.54	1.1	1.5	17	23	0.4	0.4
6	421	176	2.64	2.64	0.6	0.4	11	10	0.3	0.4
7	62.3	19.1	3.05	3.01	2	1.2	15	14	0.2	0.3
8	72.6	46.9	1.77	1.57	1.2	0.9	9	8	0.3	0.3
9	149	72.6	1.3	1.18	0.7	0.7	7	6	0.7	0.6
10	236	54.4	1.98	2.27	0.6	0.8	10	8	0.4	0.4
11	90.1	67.7	3.31	2.42	0.9	0.8	13	13	0.3	0.8
12	82	43.2	2.65	2.64	1.2	0.7	13	10	0.3	0.2
13	136	54	n/a*	2.13	1.1	0.8	9	9	0.4	0.3
14	185	64.2	1.86	1.61	1.1	0.7	6	9	0.1	0.2
15	56.3	43	1.9	2.7	1.1	0.9	9	12	0.2	0.2
Mean (median)	**185.5 (136)**	**60.5 (54.4)**	**2.31**	**2.26**	**1.10**	**0.93**	**12.46**	**12.26**	**0.41**	**0.39**
SD	138.0	35.5	0.66	0.57	0.42	0.32	5.93	5.71	0.28	0.16
p-value		< 0.001		0.71		< 0.05		0.41		0.74

Reference intervals: TT_4 = 10-45 nmol/L; SCr = 0.8-2.1 mg/dl; serum SDMA <14 µg/dl; UPC <0.4

p-values: calculated to compare difference between baseline and 6-month post-treatment values, with significance considered $p \leq 0.05$.

***Initial GFR measurement for cat 13 was measured twice on two different occasions and each time found to be >10 ml/min/kg. This value is significantly higher than any published reference interval, and was therefore removed from the statistical analysis.**

Footnotes

a. Immulite Chemiluminescent enzyme immunoassay, Siemens Healthcare, Erlangen, Germany.

b. Michigan State University Diagnostic Center for Population and Animal Health, Lansing, MI.

c. Idexx Laboratories, Westbrook, Maine.

d. HESKA Corporation, Loveland, CO.

e. Ultrasonic Doppler Flow Detector, Parks Medical Electronics Inc, Aloha, OR.

f. Bili Labstix, Bayer Healthcare LLC., Morristown, NJ.

g. Hitachi 911, Roche Diagnostics, Indianapolis, IN.

h. Ascend Laboratories, LLC, Montvale, NJ.

i. SAS, SAS Institute Inc, Cary, NC.

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Appendix A - Abbreviations

^{99m}Tc-DTPA	^{9m}Tc-labeled diethylenetriaminepentaacetic acid
CLEIA	Chemiluminescent enzyme immunoassay
CKD	Chronic kidney disease
CBC	Complete blood count
EMD	Epaxial muscle diameter
EDTA	Ethylenediaminetetraacetic acid
ERD	Semi-quantitative feline specific albuminuria assay
fT_4	Free thyroxine
fT_4ED	Free thyroxine by equilibrium dialysis
fT_3	Free triiodothyronine
GGT	Gamma-glutamyl transpeptidase
GFR	Glomerular filtration rate
KSU-VHC	Kansas State University-Veterinary Health Center
^{131}I	Radioiodine
MSU	Michigan State University
mCi	Milicuries
SCr	Serum creatinine
SDMA	Serum symmetrical dimethyl arginine
SD	Standard deviation
SBP	Systolic blood pressure
TT_3	Total triiodothyronine
TSH	Thyroid stimulating hormone
T_4	Thyroxine
TT_4	Total thyroxine
T_3	Triiodothyronine
UAC	Urine albumin to creatinine ratio
UPC	Urine protein to creatinine ratio
UGGTC	Urine gamma-glutamyl transpeptidase to creatinine ratio