

Feline Hyperthyroidism - Avoiding Further Renal Injury

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Background

In the 30 years since hyperthyroidism was initially reported by Peterson in 1979¹ we have developed numerous methods for successfully treating the disease. Surgical thyroidectomy was first described in the initial description of the disease¹ and later by numerous others²⁻¹⁰. Descriptions of medical management initially with propylthiouracil (PTU)¹¹⁻¹³ and subsequently with methimazole¹⁴⁻²⁴ followed thereafter. Radioiodine therapy using ¹³¹I was initially reported in 1984 by Turrel and has gone on to become the gold standard therapy for these patients.²⁵ Additional novel therapies including percutaneous ethanol injection²⁶⁻²⁸ and percutaneous ultrasound guided radiofrequency heat ablation²⁹ have also seen limited utility. As a result of the numerous options for treating hyperthyroidism in the cat, successful resolution of thyrotoxicosis in these patients has become common place. Ensuring the long term survival and well being of these patients remains a somewhat more complicated endeavor. Not surprisingly, ensuring long term survival for these patients involves addressing the concurrent health issues present in these geriatric patients. Common concurrent illnesses experienced by hyperthyroid cats include cardiac, neoplastic and gastrointestinal diseases.³⁰⁻³⁵ Excluding thyrotoxic cardiomyopathy, which is a largely reversible form of cardiovascular disease that is itself caused by hyperthyroidism^{33, 36}, no other single malady has exceeded the prevalence of renal insufficiency in hyperthyroid cats.³⁷⁻⁴⁰

Hyperthyroidism masks chronic kidney disease

In 1994 Graves, et. al.⁴¹ described the initial report associating renal function changes with the treatment of cats with hyperthyroidism. In his report the authors measured glomerular filtration rate (GFR) estimated by plasma disappearance of ⁹⁹Tc-labeled DTPA as well as several clinical laboratory parameters of renal function in 13 cats with naturally acquired hyperthyroidism before and after bilateral thyroidectomy. They found that the mean GFRs decreased and the mean serum creatinine increased in these cats following a resolution of their thyroid disease. In this study 15% of the cats became azotemic following a return to euthyroidism. Following this initial report numerous other authors confirmed that the changes in renal function accompanying the resolution of hyperthyroidism were independent of the method of therapy.^{40, 42, 43} Hence, regardless of the therapy chosen, a decrease in GFR should be expected upon resolution of hyperthyroidism.

All of the studies done to date that have evaluated renal function in cats treated for hyperthyroidism have concluded the following findings, 1.) the metabolic changes associated with hyperthyroidism can mask the presence of co-existing chronic kidney disease, 2.) the changes in renal parameters that follow a resolution of hyperthyroidism manifest themselves within a one month period after which ongoing measurement of renal parameters reveal relatively stable values. Initial studies failed to identify reliable parameters to predict which cats will become azotemic following resolution of their thyroid disease. Subsequently GFR as estimated by renal scintigraphy⁴⁰ was shown to have predictive value in determining which cats with hyperthyroidism will become azotemic following radioiodine therapy. More recent studies have confirmed the utility of GFR measurement in predicting which hyperthyroid cats will become azotemic following resolution of the thyroid disease. These recent studies have also shown value in more routinely available laboratory parameters including serum creatinine, urine specific gravity and T₄ levels when attempting to predict which hyperthyroid cats will become azotemic following a return to euthyroidism.⁴⁴⁻⁴⁶

Evidence that hyperthyroidism itself contributes to chronic kidney disease.

The prevalence of chronic kidney disease in the geriatric cat population has variably been reported as 7.7% of the cats over 10 years of age⁴⁷, 15.3 % of the cats over 15 years of age⁴⁸ and 30% of cats over 15 years of age⁴⁹. By comparison the prevalence of chronic kidney disease in hyperthyroid cats has been reported as ranging between 14-40%³⁷⁻⁴⁰. The higher than expected prevalence of chronic kidney disease in hyperthyroid cats suggests that thyrotoxicosis may actually contribute to the development or progression of chronic kidney disease in cats. Figure 1 illustrates the pathophysiologic steps that may allow thyrotoxicosis to contribute to the development or progression of chronic kidney disease in hyperthyroid cats.

To date two different markers of renal proximal tubular injury have been used to investigate the potential contribution of hyperthyroidism to renal injury. These markers are retinol binding protein (RBP) and N-acetyl- β -D-glucosaminidase (NAG). RBP is a serum protein that binds retinol (vitamin A). Serum RBP forms a complex with its retinol ligand. This complex binds to

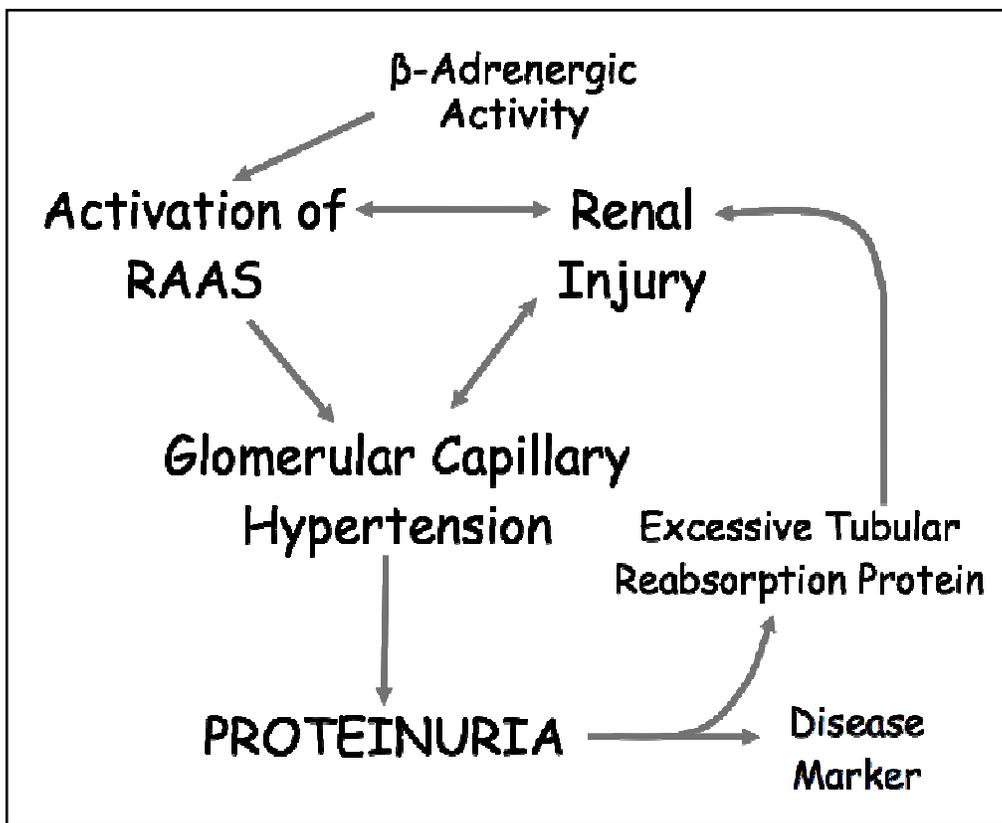


Figure 1: This graphic demonstrates the pathophysiologic steps that may result in thyrotoxicosis contributing to chronic kidney disease.

the larger protein transthyretin, which prevents the loss of both serum RBP and its bound retinol through glomerular filtration. Upon release of its ligand, the uncomplexed RBP no longer has affinity for transthyretin and can freely pass through the glomerular barrier and be reabsorbed through endocytosis in the proximal tubules. However, when tubular function fails, elimination of uRBP shifts from intratubular catabolism to urinary excretion. This tubular type of proteinuria is a highly sensitive index of renal tubular damage in humans and retinol binding protein is suggested as a clinically useful marker of renal function in cats.⁵⁰ Because urine levels of RBP (uRBP) is a marker for tubular dysfunction or damage, increased uRBP excretion may reflect

ongoing tubular damage. Cats with untreated hyperthyroidism have increased levels of uRBP. After treatment, these high uRBP levels fall in cats without azotemia suggesting that hyperthyroidism is responsible for a reversible form of renal disease. These findings have been interpreted as evidence that hyperthyroidism contributes to CKD in cats.⁵¹

Enzymuria is the presence of enzymes in urine. One potentially clinically useful urinary enzyme is N-acetyl- β -D-glucosaminidase (NAG), a lysosomal glycosidase found primarily in epithelial cells of the proximal convoluted tubule. Because urinary creatinine excretion is relatively constant over time, urinary NAG levels are expressed as a ratio over urine creatinine which yields the NAG index (U/g) (NAGi). Like uRBP, NAG is known to be a specific marker of active proximal tubular damage in many species and can be of use in the early detection of an array of renal diseases, both acute or chronic.⁵² Cats with hyperthyroidism have increased values of urinary NAG. With the return to euthyroidism increased urinary NAG levels return to normal. These findings represent additional evidence that hyperthyroidism contributes to CKD in cats.⁵³

Previously it has been suggested that hyperthyroid cats with concurrent chronic kidney disease should have their thyroid disease medically managed using methimazole with the goal of “dialing in” a mildly to moderately elevated T₄ level that would reduce symptoms of thyrotoxicosis and minimize the patient’s azotemia.⁵⁴⁻⁵⁶ More recent evidence that thyrotoxicosis from hyperthyroidism actually contributes to chronic kidney disease should prompt the therapeutic goal of euthyroidism.

Evidence that iatrogenic hypothyroidism contributes to chronic kidney disease.

To investigate the effect of hypothyroidism on renal function in dogs Panciera et. al. measured various renal parameters before and after creating iatrogenic hypothyroidism in dogs with normal renal function using radioiodine.⁵⁷ These authors found that experimentally induced iatrogenic hypothyroidism reduced GFR in dogs with previously normal renal function. To investigate the effect of reversing hypothyroidism in dogs, Gommersen et. al. measured various renal parameters before and after supplementation with oral L-thyroxine in dogs with spontaneous clinical hypothyroidism.⁵⁸ These authors found that supplementation with oral L-thyroxine at doses that achieved euthyroidism resulted in an increase in GFR in spontaneously hypothyroid dogs. To investigate the impact of iatrogenic hypothyroidism on renal function and survival time in hyperthyroid cats, Williams et. al. correlated post therapy thyroid hormone levels with renal status. They found that iatrogenic hypothyroidism appears to contribute to the development of azotemia and reduced survival after treatment of feline hyperthyroidism.⁵⁹

Documentation of iatrogenic hypothyroidism.

A total T₄ level below the low end of the reference range following therapy of any kind for hyperthyroidism is usually a good indication of iatrogenic hypothyroidism. When medical therapy is being used, this finding should prompt the reduction in methimazole dose administered to the patient. Following radioiodine (¹³¹I) therapy a transient period of hypothyroidism is common (Figure 2). This period of hypothyroidism occurs in the period following the death of the adenomatous thyroid tissues responsible for the hyperthyroidism and before regeneration of previously suppressed normal thyroid tissue by the increased TSH released by the pituitary gland in response to the hypothyroidism.⁶⁰ The duration of this period is usually measured in days to weeks and may be completely clinically silent. However, depending on the degree of suppression or damage to normal thyroid tissues, this transient period may be clinically detected. In cats with normal renal function this period is generally monitored by periodic total T₄ measurement without intervention. Supplementation with oral thyroid hormones (i.e., L-thyroxine) during this period will rapidly resolve the iatrogenic

hypothyroidism but will also prevent the persistent TSH production by the pituitary gland needed

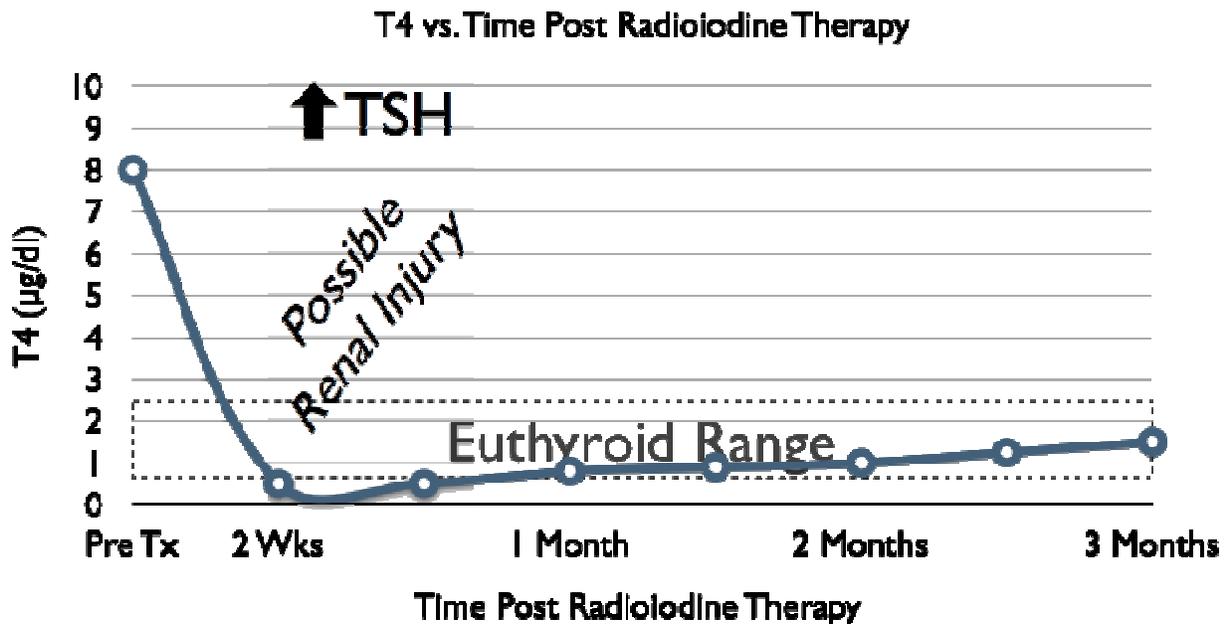


Figure 2: T4 versus time post radioiodine therapy for a typical hyperthyroid cat. Notice the transient decline in serum total T4 that follows the resolution of the adenomatous thyroid disease causing hyperthyroidism. This period is accompanied by increased TSH release resulting in the stimulation of the previously suppressed normal thyroid tissue and ultimately in the return to chronic euthyroidism.

to stimulate regeneration of previously suppressed normal thyroid tissue. Therefore unless cats with normal renal function demonstrate other overt symptoms of this transient hypothyroidism (e.g., anemia, lethargy), supplementation is generally avoided. However cats with preexisting renal dysfunction will potentially experience a further worsening of chronic kidney disease during this period of iatrogenic hypothyroidism.⁵⁹ As a result, supplementation with L-thyroxine for cats with iatrogenic hypothyroidism and concurrent chronic kidney disease is generally indicated.

The diagnosis of iatrogenic hypothyroidism in cats with concurrent chronic kidney disease and associated azotemia can be complicated as cats are just as susceptible to euthyroid sick syndrome as dogs.^{61, 62} While thyroid stimulating hormone (TSH) measurement is routinely used for diagnosing thyroid disease in man and dogs, it is not routinely used in cats as no feline specific assay is currently available. Furthermore, the canine TSH assay has shown a limited sensitivity for measuring feline TSH levels at the low end of the assay. Despite these limitations, measurement of TSH levels using the canine specific assay (cTSH) can provide limited information about thyroid function in cats. Because the assay has a reasonable validity at the high end of the range, the combination of an increased cTSH with low total T4/FT4 levels in a post radioiodine therapy cat is consistent with the diagnosis of iatrogenic hypothyroidism. However, because the cTSH assay is a canine specific test, reference laboratories do not provide feline specific reference ranges. As a result, familiarity with the reference range of cTSH for healthy geriatric cats (< 0.03-0.15 ng/ml) determined by Wakeling is required.⁶³

Recommendations

We have seen that in hyperthyroidism the renal autoregulatory mechanisms can become dysfunctional resulting in a local activation of the Renin, Angiotensin, Aldosterone System. This activation can then lead to hyperfiltration and subsequent glomerular hypertension ultimately leading to proteinuria. This proteinuria leads to increased tubular protein resorption and further renal injury.

These findings suggest that leaving the hyperthyroid state untreated may be detrimental to renal function. For this reason resolving thyrotoxicosis, even in cats with concurrent CRF, may help preserve remaining kidney function. However the reduction in GFR that accompanies a resolution of thyrotoxicosis should be anticipated and standard supportive therapies for pre-existing renal disease should be initiated to ensure tolerance for the incremental change in renal function that accompany the return to euthyroidism. Most cats with concurrent CKD and hyperthyroidism will benefit from the administration of subcutaneous fluids following the initiation of antithyroid therapy. Many cats will benefit from the initiation of other standard therapies including possible dietary phosphorus restriction, phosphate binders, H₂ blockers, calcitriol, potassium gluconate, antihypertensive therapy (as indicated by confirmation of hypertension), benazepril (as indicated by confirmation of proteinuria), and supplemental B-vitamin administration.

We have also shown that iatrogenic hypothyroidism has the potential to reduce GFR and hence significantly exacerbate preexisting chronic kidney disease. As a result when treating cats with concurrent chronic kidney disease for hyperthyroidism every effort should be made to avoid iatrogenic hypothyroidism. Conservative doses of methimazole and customized doses of radioiodine (¹³¹I) should be utilized when treating cats with hyperthyroidism and concurrent chronic kidney disease. Since the detection of concurrent renal disease is challenging in hyperthyroid cats, the insurance of chronic euthyroidism is critical when managing these patients.

Most articles have shown that hyperthyroid cats with concurrent chronic kidney disease will

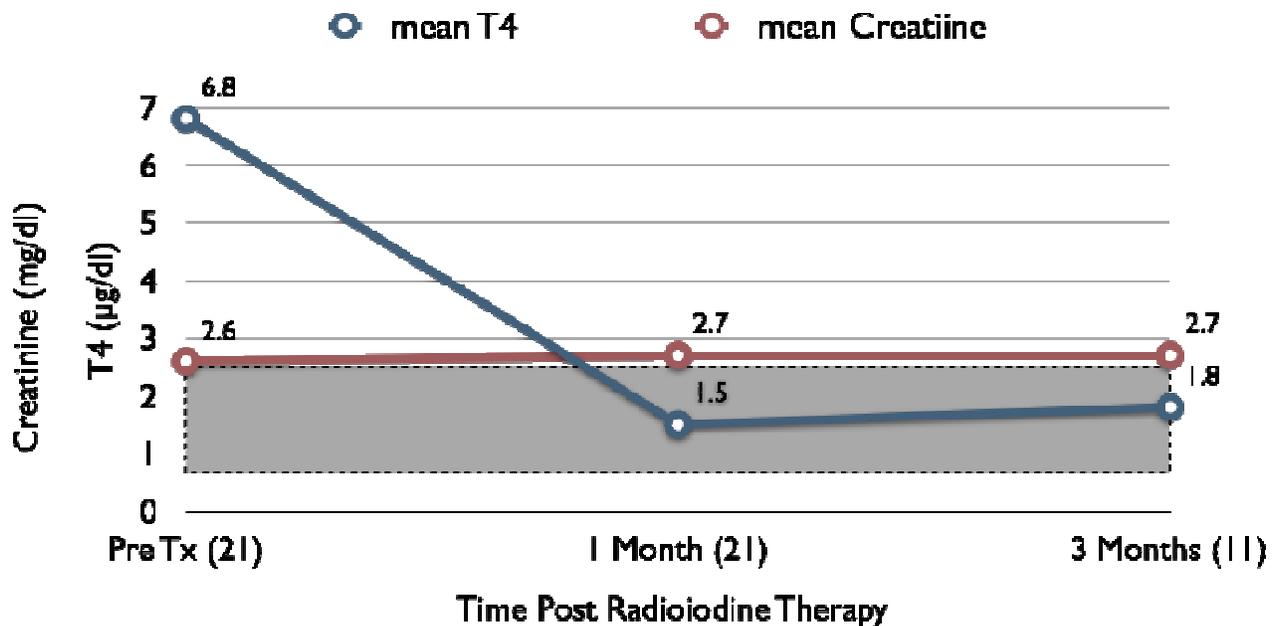


Figure 3: T4 and creatinine verses time post radioiodine therapy for a series of 22 hyperthyroid cats in stage 2-3 IRIS chronic kidney disease that were given 0.1 mg L-thyroxine PO q24h beginning at discharge following ¹³¹I therapy. Note the minimal impact on renal function that is achieved by avoiding a period of post treatment iatrogenic hypothyroidism.

demonstrate a mild increase in creatinine following a return to euthyroidism. This increase in creatinine is due to the decreased GFR that accompanies the reduced cardiac output and renal blood flow in these patients following a return to euthyroidism. In the large majority of cases, this increase in creatinine is well tolerated. Even cats that became azotemic as a result of this decrease in GFR generally demonstrate evidence of marked clinical improvement including cessation of gastrointestinal (i.e., vomiting and diarrhea) symptoms and weight gain.

Occasionally cats with pre-existing chronic kidney disease will demonstrate a more overt deterioration in kidney function following the initiation of therapy for hyperthyroidism leading to a potentially life limiting uremia. It is this author's opinion that the majority of these cases are caused by periods of iatrogenic hypothyroidism that contribute to further renal function decline.

As a result it is of paramount importance that iatrogenic hypothyroidism should be avoided when treating hyperthyroid cats with preexisting chronic kidney disease. These patient's reduced renal function might be irreversibly exacerbated by the physiologic changes that accompany hypothyroidism. To avoid iatrogenic hypothyroidism when treating hyperthyroid cats with concurrent chronic kidney disease we have adapted a therapeutic protocol that ensures resolution of the patient's thyrotoxicosis while avoiding even transient hypothyroidism. This therapeutic approach involves the use of customized radioiodine therapy doses followed by supplementation with oral L-thyroxine that is initiated at discharge from the hospitalization required for radioiodine therapy. Preliminary evaluation of 22 cats with stage 2-3 IRIS chronic kidney disease and pretreatment serum creatinine levels of 1.7-3.3 (mean = 2.6 mg/dl) treated with customized doses of radioiodine ranging between 1-5 mCi (mean = 2.9 mCi) and discharged on oral L-thyroxine (at 0.1 mg PO q24h) confirmed the avoidance of iatrogenic hypothyroidism and minimal associated worsening in azotemia (Figure 3). In these patients the supplementation with physiologic levels of thyroxine on discharge from the hospitalization needed for radioiodine therapy ensures that the incremental decrease in GFR that accompanies resolution of thyrotoxicosis will not be accompanied by additional renal injury caused by iatrogenic hypothyroidism.

Supplementation with oral L-thyroxine is **not** needed following radioiodine therapy in the majority of hyperthyroid cats including those with normal kidneys or mild (\leq IRIS stage I) kidney disease. In the majority of cats the transient period of hypothyroidism that follows resolution of their autonomously functional, adenomatous thyroid disease will result in increased TSH production by the pituitary leading to reactivation and regeneration of the chronically suppressed and atrophic normal thyroid tissue ultimately leading to a return to chronic euthyroidism. However, cats demonstrating protracted periods of iatrogenic hypothyroidism following radioiodine therapy with evidence of concurrent chronic kidney disease will benefit from L-thyroxine supplementation. Furthermore proactive supplementation with oral L-thyroxine at discharge following hospitalization for radioiodine therapy in hyperthyroid cats with IRIS stage 2-3 chronic kidney disease has been shown to minimize further decline in renal function following a return to euthyroidism, presumably by avoiding a period of post therapy hypothyroidism.

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