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Effects of feline hyperthyroidism on kidney function: a review

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Abstract

Chronic kidney disease and hyperthyroidism are two commonly diagnosed conditions in the geriatric feline population, and are often seen concurrently. Management of both diseases is recommended; however, the physiologic implications of both diseases must be understood to ensure the most favorable outcome for each patient. This report reviews the complex interplay between hyperthyroidism and kidney function, as well as the effects of hyperthyroid therapy on kidney function.

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Introduction

Feline chronic kidney disease

Hyperthyroidism and chronic kidney disease (CKD) are common diseases in the geriatric feline population, and the frequency of concurrent hyperthyroidism and CKD in cats increases with age.[1,2] CKD is estimated to affect 1–3% of all cats,[3] and >30% of cats older than 15 years of age.[4] 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 and continues to damage 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 concentration, proteinuria and systolic blood pressure to help guide appropriate therapy, as well as prognosis.[3] 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 (serum creatinine concentrations between 2.3 mg/dl [203 µmol/l] and 2.8 mg/dl [250 µmol/l]) had a median survival time of 1151 days, while cats with IRIS CKD stages 3 (serum creatinine concentrations between 2.9 mg/dl [251 µmol/l] and 5.0 mg/dl [440 µmol/l]) or 4 (serum creatinine concentrations >5.0 mg/dl [>440 µmol/l]) had a median survival time of 679 and 35 days, respectively.[5] 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.

Feline hyperthyroidism

The diagnosis of feline hyperthyroidism has increased steadily since its recognition in the late 1970s, and is now the most common endocrinopathy affecting older cats. The prevalence of hyperthyroidism in a population of cats older than 9 years of age was recently reported to be 6%.[6] The etiology of hyperthyroidism is not completely understood, but is likely multifactorial. The majority of cats with hyperthyroidism have a functional adenoma, of one or both of the thyroid glands, that will continue to grow over time.[7] Bilateral disease occurs in approximately 70% of cases.[8] Approximately 3% of hyperthyroid cats are found to have thyroid carcinoma.[9]

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Within the thyroid gland, iodine from the diet is the major constituent used in the production of triiodothyronine (T3) and thyroxine (T4), which are stored in the thyroid follicles until thyroid-stimulating hormone (TSH) from the pars distalis of the pituitary gland stimulates their release. More than 90% of released thyroid hormone is T4; however, almost all T4 is eventually deiodinated to T3 at a cellular level. T3 is the biologically active form of thyroid hormone, and is approximately four-fold more potent than T4.[10] The physiologic effects of thyroid hormone are widespread and the net result of an overactive thyroid gland is a syndrome of hypermetabolism. The reported median survival time for cats with hyperthyroidism ranges from 1.6–4.0 years,[2,11–13] while cats classified as having CKD prior to treatment of hyperthyroidism have shorter survival times of 0.5–2.0 years.[2,13]

Effects of thyrotoxicosis on the kidney

Thyrotoxicosis leads to hemodynamic changes throughout the body, many of which specifically affect the kidneys. For example, humans and cats with naturally occurring hyperthyroidism have activation of the renin–angiotensin–aldosterone system (RAAS).[14,15] Elevations in T3 (the biologically active thyroid hormone) not only have a direct effect on renin gene expression, but also act directly on vascular smooth muscle cells, causing relaxation and decreased peripheral vascular resistance by as much as 50%.[14,16–18] 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.[14,16] As the blood volume increases, so does cardiac preload, which, in combination with the decreased systemic vascular resistance, results in an increase in cardiac output of 60% or more.[16,18]

In addition, hyperthyroidism may be associated with increased responsiveness, and upregulation of β-adrenergic receptors within cardiac tissue, as well as the renal cortex,[19] that can lead to increased sympathetic nervous system activity and increased RAAS activity.[14] The resulting increase in heart rate and left ventricular contractility also has the potential to contribute to increased cardiac output.[18] Hyperthyroid-associated decreased vascular resistance, in combination with increased cardiac output, and overall increased blood volume, lead to increased renal blood flow (RBF), increased glomerular capillary hydrostatic pressure and increased glomerular filtration rate (GFR). Additionally, GFR upregulation is enhanced secondarily to thyroid hormone-induced increases in expression of messenger RNAs encoding for chloride channels, leading to increased chloride absorption in the proximal tubule and loop of Henle.[20] 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.[13,21] Increases in proteinuria associated with CKD have been hypothesized to occur secondarily to increased glomerular capillary pressure and impaired tubular resorptive capacity of remaining nephrons.[22,23] Although the mechanism of proteinuria in hyperthyroidism is incompletely understood, clinically significant systemic hypertension due to hyperthyroidism is less common than initially thought;[13,24] 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 and the progression of azotemic CKD.[25,26] Fortunately, the magnitude of proteinuria tends to decrease once the euthyroid state is restored.[13,27]

The presence or absence of azotemia (assessed via serum creatinine and serum blood urea nitrogen [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 interpretation of 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 pretreatment 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%,[2,13,28] while post-treatment azotemia occurs in approximately 15–49% of hyperthyroid cats.[2,13,29]

Effects of hyperthyroidism treatment on kidney function

There are multiple options available for the treatment of feline hyperthyroidism, including medical management with oral antithyroid medication (methimazole), and curative treatments such as radioiodine (^{131}I) and thyroidectomy. 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.[12,21,29–33] 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 of treatment.[31] 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.[29] Conversely, GFR decreased significantly at 1 month after treatment, and continued to decrease to 6 months after treatment, although the decrease beyond 1 month was not significant.[29] Similar results were observed in another study in which GFR decreased significantly until 4 weeks post-^{131}I treatment and then stabilized.[21] 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.[13] 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 non-azotemic.[34] However, cats with azotemia prior to initiation of treatment for hyperthyroidism appear to have decreased survival compared with cats that become azotemic following treatment.[2,13]

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. Although renal function tends to stabilize, it is advisable for clinicians to monitor serum creatinine concentration for at least 6 months after the cat has became euthyroid.

Effects of hypothyroidism on the kidney

Hypothyroidism has been associated with decreased GFR in dogs,[35] and similar physiology is suspected in cats. Diminished GFR could have significant consequences for hyperthyroid cats with pre-existing renal disease that become hypothyroid as a result of treatment. In 80 hyperthyroid cats treated either with antithyroid medication alone or in combination with thyroidectomy, 28 were diagnosed with hypothyroidism 6 months post-therapy based on decreased total T4 concentration and increased TSH concentration.[34] 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 non-azotemic hypothyroid cats.[34] Thus, cats with iatrogenic hypothyroidism are not only more likely to develop azotemia, but hypothyroid cats with azotemia also have decreased survival.[34] Supplementing cats with iatrogenic hypothyroidism secondary to ^{131}I with thyroid hormone, or reducing the dosage of antithyroid medication, to achieve a euthyroid state, may improve renal function. This recommendation is based on resolution of azotemia in 50% of hypothyroid cats in which hypothyroidism was corrected by a decrease in the dose of antithyroid medication.[36]

Based on these findings, the importance of identifying and treating cats with iatrogenic hypothyroidism becomes apparent. Inasmuch as hypothyroidism may not occur for as long as 3–6 months after radioiodine treatment,[34] it is important to continue to monitor total T4 for at least 6 months post-treatment. A low total T4 concentration alone is not sufficient for diagnosis of iatrogenic hypothyroidism owing to the potential for euthyroid sick syndrome.[37] The combination of reduced total T4 concentration and elevated TSH concentration is consistent with iatrogenic hypothyroidism. In this circumstance, T4 supplementation or adjustment of antithyroid medication should be considered.[37]

Pretreatment predictors of post-treatment azotemia

Although the prognosis for cats that develop post-treatment azotemia is similar to hyperthyroid-treated cats that remain non-azotemic,[34] 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 urine specific gravity have not been shown to predict development of azotemia reliably after treatment of hyperthyroidism.[1,12,28,29,32,38] In one large study, plasma concentrations of urea and creatinine were positively correlated, and plasma globulin concentration was negatively correlated with the development of post-treatment azotemia;[13] however, other studies have not confirmed these results. Pretreatment measurement of GFR has shown promise for predicting post-treatment azotemia in some studies;[31] however, other studies have shown significant overlap in GFR values.[21] 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, the mechanism of which is incompletely understood. Regardless of the underlying mechanism, successful treatment of hyperthyroidism leads to a significant decrease in urinary protein excretion as assessed by urine protein:creatinine ratio (UPC) 4 weeks post-treatment.[13,21] In contrast to the UPC, one study demonstrated that the urine albumin to creatinine ratio did not decrease with successful treatment of hyperthyroidism, suggesting that albuminuria may not be a major contributor to the proteinuria observed in hyperthyroid cats.[13] 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.[13,21]

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.[39] 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 pretreatment NAG_i did not differentiate azotemic euthyroid cats from non-azotemic euthyroid cats after treatment.[40] 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.[40]

Urinary retinol binding protein (uRBP) is a sensitive indicator of renal tubular damage in humans, with minor tubular dysfunction leading to increased urinary excretion of uRBP.[41] 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.[42] 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.[43] These data suggest 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.[43]

As previously discussed, there is increased activation of the RAAS in hyperthyroid cats.[15] The subsequent elevations in angiotensin II, which preferentially constricts the efferent glomerular arteriole, may lead to decreased peritubular blood flow and peritubular hypoxia. Vascular endothelial growth factor (VEGF) is a regulator of blood vessel growth, and in humans is produced by renal proximal tubular cells in response to hypoxia in vitro.[44] 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.[45] 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 CKD post-treatment, and thus tubular hypoxia may not be a mechanism for renal damage in hyperthyroid cats.[45]

Conclusions

To date, no single readily available serum or urinary biomarker is able to predict post-treatment renal function reliably in hyperthyroid cats.[12,13,28,29,31,32,38] 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 pretherapy CKD should be discussed with owners, and continued monitoring of renal function for months following the return to euthyroidism is necessary. In addition, owing 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 antithyroid medication or thyroid supplementation when necessary.

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