

## Cardiovascular and Renal Manifestations of Hyperthyroidism

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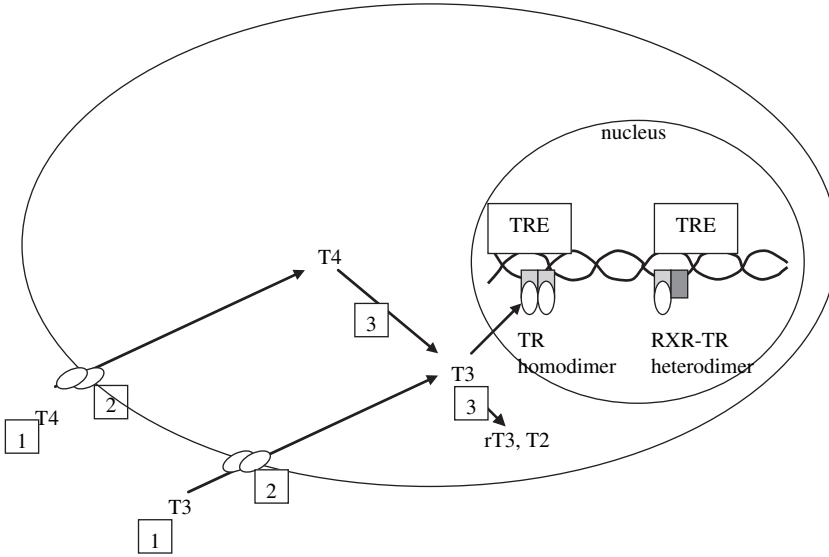
In the simplest terms, hyperthyroidism is the clinical syndrome that results from an excess of thyroid hormones. This review considers the effects of hyperthyroidism on the cardiovascular and renal systems by reviewing the available literature on the clinical manifestations of this syndrome in the cat and also considering experimental studies and experience in other species, including human beings.

### MECHANISMS OF THYROID HORMONE ACTION IN TARGET TISSUES

To understand the alterations in organ function that occur as a result of hyperthyroidism, it is necessary to review the mechanisms by which thyroid hormones act within the cell. Although thyroxine ( $T_4$ ) is the major product secreted by the follicular cells of the thyroid gland, it is the metabolite triiodothyronine ( $T_3$ ) that is responsible for the main hormonal activity. The biologic activity of thyroid hormone is controlled by the intracellular  $T_3$  concentration. This, in turn, depends on the concentrations of the circulating thyroid hormones  $T_3$  and  $T_4$ , factors controlling the entry of these hormones into cells, and the activity of deiodinase enzymes within the cell that can convert the prohormone  $T_4$  into  $T_3$  or convert the hormones into inactive metabolites (Fig. 1).

Although it was originally presumed that thyroid hormones simply passed through the cell membrane because of their lipophilic structure, it is now known that most thyroid hormone passes through the cell membrane by means of specific transporters, several of which have been characterized [1]. In general, the transporters responsible for thyroid hormone uptake into the cell are organic anion transporters and amino acid transporters. Expression of some of these transporters is tissue specific, resulting in one mechanism for control of intracellular thyroid hormone availability.

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**Fig. 1.** Mechanisms for control of thyroid hormone activity within target tissue. (1) Concentration of circulating T<sub>4</sub> and T<sub>3</sub> is controlled by the thyroid gland and the peripheral actions of 5'-deiodinase type 1. (2) Entry of thyroid hormones into cells is controlled by specific membrane transporters. (3) Conversion of the prohormone T<sub>4</sub> into T<sub>3</sub> and of T<sub>3</sub> into inactive metabolites is, in turn, controlled by 5'-deiodinase enzymes (types 2 and 3). TR, thyroid receptor; TRE, thyroid hormone response element; RXR, retinoid X receptor.

Once thyroid hormone has entered the target cell, it may exert its biologic effects (T<sub>3</sub>), be converted from an inactive precursor (T<sub>4</sub>) into active hormone (T<sub>3</sub>), or be metabolized (T<sub>4</sub> or T<sub>3</sub>) into inactive hormones (rT<sub>3</sub> or T<sub>2</sub>). All these conversions are controlled by iodothyronine deiodinase enzymes, a family of selenoproteins that catalyze the removal of specific iodine moieties from thyroid hormones. Deiodinases seem to be of critical importance in development, ensuring that there is regulated and coordinated exposure of specific tissues to thyroid hormones at different times. Expression of different deiodinase enzymes is, at least in part, responsible for the variable sensitivity of different tissues to thyroid hormones, because the intracellular production of T<sub>3</sub> is low in some tissues. There are recognized species differences in the tissue distribution and substrate selectivity of the deiodinase enzymes [2].

The classic mechanism of thyroid hormone action once in the cell is by means of interaction with nuclear receptors that bind to regulatory regions of genes, and thus act to up- or downregulate their expression. Thyroid hormone (T<sub>3</sub>) regulates nuclear gene expression by binding to the thyroid hormone receptors, TR $\alpha$  and TR $\beta$ , each of which, in turn, has several different isoforms. At the target gene promoter, TR interacts with a distinct DNA sequence, termed the *thyroid hormone response element* (TRE), as a homodimer or, more often, as a heterodimer with retinoid X receptor (RXR) [3]. Target genes

may be positively or negatively regulated by  $T_3$ , although negative regulation seems to be more common, at least in the liver [4]. At negatively regulated TREs, unliganded TRs mediate constitutive gene expression and  $T_3$  binding induces active repression of gene transcription. Conversely, at positively regulated TREs, unliganded TRs mediate basal transcriptional repression and  $T_3$  binding stimulates the active induction of gene transcription. Numerous families of coactivator and corepressor proteins exist, and binding or displacement of these proteins serves to amplify the effect of ligand-induced transcriptional repression or activation.

Classic genomic effects of steroid hormone binding have a considerable latency with response times in hours to days. Several thyroid hormone-mediated actions are known to occur within a few minutes, however, and are therefore incompatible with the classic genomic model of action. Nongenomic actions of thyroid hormones have been described at the plasma membrane, in the cytoplasm, and in cellular organelles, particularly the mitochondrion [5]. Nongenomic effects include the modulation of ion flux into and within the cell and the activation of numerous second-messenger systems. These effects are not, however, totally independent of the genomic actions of thyroid hormone, because activation of signaling pathways by nongenomic mechanisms may result in phosphorylation of TRs, augmenting their transcriptional activity and stability.

## PHYSIOLOGIC EFFECTS OF THYROID HORMONE ON THE CARDIOVASCULAR SYSTEM

Thyroid hormones have profound effects on the cardiovascular system. Many of the clinical manifestations of hyperthyroidism are attributable to the ability of thyroid hormones to alter cardiovascular hemodynamics [6]. This has resulted in considerable study of the pathophysiologic effects of thyroid hormones on the cardiovascular system in human beings and animal models and at the cellular and molecular level.

### Heart Rate

Thyroid hormone has a consistent positive chronotropic effect, and resting sinus tachycardia is the most common cardiovascular sign of hyperthyroidism in people. Circadian rhythm is preserved and may even be exaggerated [7]. Analysis of heart rate variability in hyperthyroid human patients supports a relative decrease in parasympathetic tone [8]. Beta-blockade reduces the tachycardia but does not completely abrogate it, supporting the notion also demonstrated by cell culture experiments that thyroid hormone is directly able to increase the rate of sinus node firing [9]. A direct effect is also supported by the positive chronotropic effect of thyroid hormone in isolated denervated hearts [10].

### Autonomic Effects

The effects of sympathomimetic agents and thyroid hormones (such as increases in heart rate and contractility) are similar, and treatment of patients with beta-blockers ameliorates many of the clinical signs of hyperthyroidism. This has

resulted in the hypothesis that some of the effects of thyroid hormone are mediated by increased activity of the sympathoadrenal system, but this theory has been difficult to substantiate. Because plasma and urine catecholamine concentrations are not elevated in thyrotoxicosis [11], it has been proposed that the sensitivity of the sympathoadrenal system is increased, but investigations in this area have yielded contradictory results [12,13]. Baroreceptor function, although blunted in hypothyroidism, seems to be similar in hyperthyroid and euthyroid rats [14]. Perhaps the most convincing evidence for adrenergic hyperresponsiveness in the hyperthyroid state comes from recent studies using transgenic mice [15]. In these mice, the human type 2 iodothyronine deiodinase (D2) gene is expressed in the myocardium, resulting in mild chronic thyrotoxicosis that is limited to cardiac tissue; circulating thyroid hormone concentrations are normal. Cardiomyocytes from these D2 transgenic mice exhibit an increase in  $\beta$ -adrenergic responsiveness.

### Systemic Vascular Resistance and Blood Pressure

Thyrotoxicosis may be associated with as much as a 50% decline in systemic vascular resistance (SVR) [3].  $T_3$  causes this decrease in SVR by dilating the resistance arterioles of the peripheral circulation. This effect is greater than can be accounted for by thyroid hormone-induced increases in tissue metabolism and consequent release of locally acting vasodilators. Indeed, a direct relaxant effect of  $T_3$  on vascular smooth muscle cells has been demonstrated in isolated skeletal muscle arteries [16] and in cell culture [17]. The rapidity with which the relaxation occurs in these studies favors a nongenomic mechanism. Endothelial denudation attenuates but does not abolish the  $T_3$ -mediated effect on arteriolar tone [16]. Altered secretion of atrial natriuretic peptide and adrenergic tone may also contribute to the  $T_3$ -induced changes in vascular resistance [18].

Administration of  $T_3$  to healthy euthyroid human volunteers results in a reduction in SVR and increase in cardiac output (CO) within minutes, also supporting a nongenomic mechanism of thyroid hormone action in this setting. Supraphysiologic doses of  $T_3$  were used in those experiments, however, so the physiologic relevance of the effects is not clearly established [19].

In the clinical setting, hyperthyroidism causes only a minor reduction in mean arterial blood pressure, because decreases in diastolic pressure attributable to peripheral vasodilation are offset by increases in systolic pressure caused by increases in stroke volume [20]. The increase in heart rate that occurs in hyperthyroidism may also contribute to the observed increases in systolic arterial pressure as the result of a reduction in the dynamic compliance of the arterial tree. This is because when the heart rate is elevated, the reflected pressure wave from the peripheral arterial tree may summate with the forward pressure wave from a subsequent cardiac contraction, increasing systolic pressure [21].

### Cardiac Output

One of the predominant cardiovascular effects in hyperthyroidism is the increase in CO that occurs. This has been studied extensively in human patients

and in animal models; however, the relative contribution of alterations in peripheral hemodynamics and myocardial contractility is still the subject of some debate [21]. Although these mechanisms of action are not mutually exclusive, whether the vascular or myocardial mechanism predominates may be of clinical significance, because modulation of loading status is thought to be a more energetically favorable method for increasing cardiac performance than increases in contractility. The importance of SVR to the increase in CO that occurs in hyperthyroidism was demonstrated by an experiment in which arterial vasoconstrictors were administered to human volunteers, resulting in a decrease in CO of 34% in those with hyperthyroidism but with no net effect in euthyroid subjects [22].

As a result of the decrease in SVR that occurs with hyperthyroidism, effective arterial filling volume falls, causing stimulation of the renin-angiotensin-aldosterone system (RAAS) [23]. Activation of the RAAS, in turn, stimulates renal sodium reabsorption, leading to an increase in plasma volume. In addition, thyroid hormone stimulates erythropoietin secretion [24]. The increase in blood volume that results from these actions increases cardiac preload, and this is one mechanism by which CO is increased in hyperthyroidism. The increase in cardiac preload that occurs in thyrotoxicosis may trigger secretion of atrial natriuretic peptide, although a stimulatory effect on ANP gene transcription by  $T_3$  is also reported [25].

Within the cardiac myocyte, thyroid hormones regulate numerous genes that are intimately related to contractile function. One of the key events controlling systolic contraction and diastolic relaxation is the rate at which the free calcium concentration in the cytosol appears and disappears, limiting the availability of calcium to troponin C of the thin filament of the myofibrils. The increase in systolic contractile activity in the hyperthyroid heart is largely attributable to the increase in calcium release from the ryanodine channels in the sarcoplasmic reticulum [3,26]. Hyperthyroidism also results in a reduction in diastolic relaxation time. Numerous ion pumps play a role in the decline in cytosolic calcium concentration that controls this, but the sarcoplasmic reticulum  $Ca^{++}$  ATPase makes the greatest contribution. Expression of the gene coding for this pump (SERCA2) is markedly increased by  $T_3$  [27]. The activity of the sarcoplasmic reticulum  $Ca^{++}$  ATPase is also regulated by phospholamban, and this, in turn, is also influenced by thyroid hormones. Numerous other plasma membrane transporters (including  $Na^+/K^+$  ATPase,  $Na^+/Ca^{++}$  exchanger, and voltage-gated potassium channels) are also regulated at the translational and posttranslational levels by thyroid hormones [28]. These and other proteins modulated by thyroid hormones have been the subject of a recent review [3].

Hyperthyroidism can also alter the expression of genes encoding structural proteins within the cardiac myocyte. A typical example of  $T_3$ -induced alterations in cardiac contractile proteins is the altered myosin heavy chain isoform (from  $MHC\beta$  to  $MHC\alpha$ ) that occurs in the hearts of hyperthyroid rats, resulting in accelerated cardiac contraction [29]. In human beings and other species,

however, including the cat, in which MHC $\beta$  is the dominant isoform expressed in adult life, it is not clear whether an alteration in myosin isoform occurs to any significant extent in the hyperthyroid state [30,31]. Thyroid hormones also cause a marked change in numerous other contractile proteins, including cardiac actin, at least in rodents [32].

Although these and numerous other cellular mechanisms may contribute to an intrinsic increase in cardiac contractility in hyperthyroidism, there are studies suggesting that the consequences may be relatively trivial compared with those induced by hemodynamic alterations, predominantly driven by the decrease in SVR. In one study of human beings subjected to cardiac catheterization, left ventricular function in patients with hyperthyroidism was compared with that of volunteers who were atrially paced at identical heart rates. The authors concluded that there was no significant increase in myocardial contractility in hyperthyroid human patients independent of changes in heart rate and cardiac preload [33]. Also, experiments with rodents that have a heterotopically transplanted heart (an additional heart that is perfused from the abdominal aorta) have shown that although hyperthyroidism causes the expected increases in heart rate and switching of MHC isoforms in the native heart and the heterotopic heart, cardiac hypertrophy only develops in the native hemodynamically loaded heart [10].

## **CARDIOVASCULAR MANIFESTATIONS OF HYPERTHYROIDISM IN CATS**

Several derangements of the cardiovascular system have been reported in cats diagnosed with hyperthyroidism. As in human beings, one of the more consistently documented abnormalities is tachycardia. This is reportedly found in approximately half of all hyperthyroid cats at presentation, although it seems that its prevalence is decreasing, presumably because of earlier diagnosis of the disease [34–36].

Systolic murmurs and gallop rhythms are frequently documented in hyperthyroid cats [36,37]. Hyperkinetic femoral pulses and a prominent left apical precordial beat are also common physical examination findings [37]. Murmurs are most often grade I to grade III/VI, and their intensity often varies with heart rate. In older reports, the murmurs were generally attributed to mitral or tricuspid regurgitation [37,38]. More recently, the murmurs have often been documented with color-flow Doppler echocardiography as being caused by dynamic left or right ventricular outflow tract obstruction [39,40]. The gallop rhythm is attributed to rapid ventricular filling.

Respiratory abnormalities, particularly tachypnea and panting, are relatively common clinical findings and may be precipitated by the stress of visiting the veterinary clinic or the physical examination process itself [36]. It is important to recognize that not all hyperthyroid cats with tachypnea or dyspnea actually have overt congestive heart failure (CHF). Causes for the respiratory signs are likely multifactorial, including heat intolerance as well as a decreased ability to increase the already elevated CO in response to stress or exercise. Exertional

dyspnea in hyperthyroid human patients is often related to weakness of the respiratory muscles rather than to cardiac abnormalities [3].

### Electrocardiography

Various ECG changes have been described with feline hyperthyroidism. The most common finding is sinus tachycardia, although with earlier diagnosis of the disease, the frequency of this finding is decreasing [35]. Other arrhythmias are also documented, although at a relatively low frequency, including atrial and ventricular arrhythmias and intraventricular conduction defects. The sinus tachycardia usually resolves with treatment for hyperthyroidism, but resolution of the other arrhythmias is less consistent. Coincident disease may be responsible for at least some of the observed abnormalities in this geriatric population of cats and, at least in some instances, the arrhythmias may not be directly related to hyperthyroidism. In people, the prevalence of atrial fibrillation and atrial tachycardia is increased in patients with hyperthyroidism compared with age-matched controls and falls with antithyroid therapy, but the prevalence of ventricular arrhythmias and conduction disturbances is not different in the two populations and does not alter with therapy [41].

The amplitude and duration of the P-QRS-T complexes may be abnormal in hyperthyroid cats. An increase in R-wave amplitude (0.9 mV) was observed in 29% of cats examined by one group in 1979 to 1982 [38], but this abnormality was only found in 8% of cats at the same institution in 1992 to 1993 [35]. The correlation between increased R-wave amplitude and radiographic or echocardiographic evidence of left ventricular enlargement in hyperthyroid cats was found to be poor in one study [42].

### Diagnostic Imaging

Thoracic radiographs may show evidence of left-sided cardiomegaly in cats with hyperthyroidism, and in a small proportion, there is evidence of CHF. Echocardiographic abnormalities classically associated with hyperthyroidism include left ventricular hypertrophy, left atrial and ventricular dilation, and increased fractional shortening [37]. It is important to realize, however, that alterations in ventricular wall thickness and chamber dimensions are typically subtle in hyperthyroid cats; indeed, most echocardiographic measurements are within the normal range [39,43–45]. Consistent with this observation, changes in chamber dimension and wall thickness associated with establishment of euthyroidism are usually small [39,43]. The variable that is most consistently decreased by treatment is the fractional shortening [39,44].

It is helpful to consider that from a pathophysiologic standpoint, the anticipated changes that occur with hyperthyroidism are those of volume loading of the left ventricle (eccentric hypertrophy) [46]. This occurs because of an increase in blood volume, together with a shift from the arterial compartment to the venous compartment, resulting in an increase in cardiac preload. Therefore increases in chamber dimension may occur, together with hypertrophy of the ventricular wall, but this is expected to be mild. If marked cardiac hypertrophy is evident, particularly if the ventricular lumen is diminished, the

possibility of concurrent idiopathic hypertrophic cardiomyopathy and hyperthyroidism should be considered.

### Congestive Heart Failure

The prevalence of CHF in cats with hyperthyroidism also seems to be declining. In cats diagnosed with hyperthyroidism at the Animal Medical Center in New York, CHF was present in 12% of cats in the early 1980s [38] but in only 2% in 1992 to 1993 [34]. Similarly, a study in the United Kingdom found that only 4 (3.1%) of 126 cats diagnosed with hyperthyroidism had CHF, and 2 of these 4 cats had concurrent intrinsic cardiac disease [36]. Taken together, these reports suggest that hyperthyroidism is an uncommon cause of cardiac failure in the absence of preexisting cardiac disease. The volume loading that occurs with hyperthyroidism may readily decompensate preexisting subclinical heart disease, however.

CHF occurs infrequently in hyperthyroid human patients. It may be precipitated by the development of atrial fibrillation, which is of particular hemodynamic significance with the short duration of diastole that occurs at high heart rates. Occasionally, CHF may develop as a result of “rate-related cardiomyopathy” [6]. Pulmonary hypertension and, occasionally, right heart failure have also been associated with thyrotoxicosis [47].

Circulating cardiac troponin I (cTnI) is a sensitive and specific marker for myocyte damage and is increased in cats with hypertrophic cardiomyopathy [48,49]. Troponin I has also been measured in hyperthyroid cats and was elevated infrequently, although none of the cats tested had CHF [39]. Cats with detectable cTnI in that study tended to have higher thyroid hormone concentrations.

### Blood Pressure

Hyperthyroidism is frequently cited as an important cause of systemic hypertension in cats. Studies of cats presenting with hypertensive retinopathy or chorioidopathy have included only a few cats with hyperthyroidism, however, suggesting that extreme elevation of blood pressure may be relatively infrequent with this condition [50–52]. Similarly, ocular examinations performed in a large series of hyperthyroid cats did not identify changes consistent with hypertension [53].

Older studies measuring blood pressure of hyperthyroid cats indicated that hypertension was common [54,55]. The number of cats included in these studies was small, however, and, in the study by Kobayashi and colleagues [54], the cutpoint for diagnosing systemic hypertension was low. More recently, two studies of blood pressure measurement in hyperthyroid cats have been reported as scientific abstracts, although neither has been published in full [56,57]. In the first of these studies, cats were examined in a referral practice before radioactive iodine therapy [56]. When blood pressure was measured using a Doppler method by a single experienced operator in a quiet environment, only 19% of the cats were found to have systolic blood pressure measurements greater than 160 mm Hg. When blood pressure was measured in an



uncontrolled manner, however, the prevalence of hypertension was much higher, suggesting that this population is particularly susceptible to the effects of “white-coat” hypertension. The second study was of 100 sequentially diagnosed hyperthyroid cats evaluated in first-opinion practice [57]. Of these cats, only 9 were hypertensive (5 of 9 had ocular lesions) at the time the hyperthyroidism was diagnosed. In addition, 3 cats were receiving amlodipine for previously diagnosed hypertension. These results indicate that hypertension is less common in cats with hyperthyroidism than has been previously supposed. This is in accordance with the observation from experimental studies, and from studies in human patients, that SVR is markedly reduced in hyperthyroidism, resulting in a reduction in diastolic blood pressure, and that although CO is elevated, increases in systolic blood pressure are typically modest.

Interestingly, a proportion of cats actually seem to develop hypertension after treatment for hyperthyroidism [57]. Initial indications are that this occurs in approximately 20% to 25% of cases. This finding needs to be substantiated by following the blood pressure of a larger number of cats during treatment for hyperthyroidism. It is unclear whether this change is associated with the decline in renal function that occurs as euthyroidism is achieved, although the development of hypertension with treatment has not been limited to cats that become azotemic with treatment. A study of the RAAS system did not show any marked differences between cats that developed hypertension and those that remained normotensive [58].

## TREATMENT FOR THE CARDIOVASCULAR MANIFESTATIONS OF HYPERTHYROIDISM

Treatment considerations are primarily centered on control of the underlying hyperthyroid state rather than on directly addressing its cardiovascular consequences. Cardiovascular effects of hyperthyroidism may influence the choice of treatment modality (radioactive iodine, antithyroid drugs, or surgical thyroidectomy). In general, provided that antithyroidal drugs are well tolerated, it is sensible to stabilize the condition of hyperthyroid patients before general anesthesia, because a high occurrence of catecholamine-induced arrhythmias has been reported in this clinical setting. If treatment with thiourylenes (methimazole or carbimazole) results in unacceptable side effects, treatment with beta-blockers is usually successful in reversing many of the cardiovascular effects of hyperthyroidism in the short term.

## RENAL MANIFESTATIONS OF HYPERTHYROIDISM

The alterations in renal function that occur in the cat coincident with changes in thyroid status are a source of great clinical concern to veterinarians. In contrast, changes in renal function are barely considered in human medicine, although similar changes do occur. This lack of clinical interest is probably attributable to the low incidence of chronic renal failure in the general human population, compounded by the fact that many people are only middle aged when they develop thyrotoxicosis. As a result of this lack of clinical interest,

there has been relatively little basic research into the effect of thyroid hormones on renal function, and much of this has focused on the effects of hypothyroidism rather than hyperthyroidism.

## **PHYSIOLOGIC EFFECTS OF THYROID HORMONES ON THE RENAL SYSTEM**

### **Renal Hypertrophy**

Hyperthyroidism increases the kidney-to-body weight ratio in rats. The mechanism is not well understood, but the participation of the renin-angiotensin system (RAS) has been proposed [59,60]. As a result of renal hypertrophy, interpretation of experimental studies in which the glomerular filtration rate (GFR) has been measured is complicated, because in some studies, the GFR apparently decreases in hyperthyroidism, but this is attributable to normalization of results per gram of renal tissue.

### **Renal Hemodynamics and Glomerular Filtration Rate**

Activation of the RAS has been implicated as a mechanism for the alteration in renal hemodynamics that occurs in the hyperthyroid state. Plasma renin activity (PRA) and plasma concentrations of angiotensin II and aldosterone are increased in experimental hyperthyroidism [61]. RAS activation has also been demonstrated in cats with naturally occurring hyperthyroidism [58]. Local tissue-specific regulation of angiotensin-converting enzyme (ACE) may also be important in the thyroid hormone-induced alterations in renal hemodynamics [60]. It has been suggested that RAS activation may be mediated, at least in part, by changes in  $\beta$ -adrenergic activity, because this is known to increase renin activity. An increase in  $\beta$ -adrenoceptor density within the renal cortex in hyperthyroidism has been reported [62]. Renal denervation does not prevent the  $T_4$ -induced increase in renin activity [63], however, and it has been shown that the renin gene has a TRE [64].

Increases in renal perfusion pressure usually result in increases in water and sodium excretion, a phenomenon referred to as the “pressure-diuresis-natriuresis response.” This mechanism is thought to be a central component of the feedback mechanism responsible for controlling extracellular fluid volume and arterial pressure. In hyperthyroid rats, the pressure-diuresis-natriuresis mechanism is impaired, such that at any given renal perfusion pressure, less sodium is excreted than in control animals [65]. This may occur because of increased renal tubular reabsorption of sodium. This seems to explain how plasma volume can increase and sodium excretion can decrease in the hyperthyroid state in spite of increases in renal blood flow and GFR. Thyroid hormones also have been shown to enhance tubular reabsorption of other electrolytes, including phosphorus [66] and chloride [67].

### **Role of Thyroid Hormone in the Progression of Experimental Nephropathy**

Thyroidectomy has been shown to reduce proteinuria and slow the progressive deterioration in renal function that occurs in rats with induced renal

insufficiency [68]. Amelioration of proteinuria by thyroidectomy has also been confirmed by other studies [69]. Reduction in proteinuria may occur as a result of changes in glomerular hemodynamics or alteration in proximal tubular protein reabsorption. Hemodynamic mechanisms may predominate in hypothyroidism, because a demonstrable decline in single-nephron glomerular filtration rate (SNGFR) and glomerular capillary pressure occurs in hypothyroid compared with euthyroid rats [69].

Conversely, hyperthyroid rats show increased renal protein excretion. In a study in which aminoguanidine (an inhibitor of inducible nitric oxide synthase [iNOS]) was administered to hyperthyroid rats, a marked increase in blood pressure was noted, but there was no corresponding increase in proteinuria, leading the authors of the study to conclude that the proteinuria occurring in hyperthyroidism does not have a hemodynamic cause [70]. Instead, the authors of the study proposed that the proteinuria occurring in hyperthyroidism may be attributable to a direct effect on the permeability of the glomerular barrier. An alternative explanation would be that the alterations in renal hemodynamics occurring in hyperthyroidism do not directly reflect those of the systemic circulation. The cause of proteinuria in hyperthyroidism should be considered unresolved.

## RENAL MANIFESTATIONS OF HYPERTHYROIDISM IN CATS

### Glomerular Filtration Rate

Several studies have been performed on cats and show that GFR decreases with treatment for hyperthyroidism. This has been demonstrated to occur with all treatment modalities (radioactive iodine, surgery, and medical treatment) [71–73] and should be considered to occur as a consequence of resolution of the hyperthyroid state rather than as a side effect of treatment. The decline in GFR is detectable 1 month after treatment for hyperthyroidism but then remains stable for at least 6 months [71]. It has also been shown that GFR and effective renal blood flow increase when normal cats are treated with exogenous thyroid hormone [74].

### Urea and Creatinine

Urea and creatinine concentrations are inversely related to GFR; therefore, values typically increase after treatment of hyperthyroidism as GFR falls. Increases in creatinine concentration occur fairly consistently in hyperthyroid cats after treatment, although in many instances, these increases occur within the laboratory reference range. Creatinine concentration is also reflective of the patient's muscle mass; thus, in an emaciated hyperthyroid patient, the creatinine concentration may be low for several reasons before treatment.

Assessment of urea concentrations in hyperthyroid cats is more complicated. Urea concentrations tend to be decreased by hyperthyroidism because of the effects on GFR, but an increase in dietary protein intake and protein catabolism may tend to increase urea concentration. For this reason urea/creatinine ratios tend to be increased in hyperthyroid cats and to normalize with treatment

(Lucie Goodwin, unpublished data, 2005). Mild elevation of urea is common in untreated hyperthyroid cats and is poorly correlated with the development of significant azotemia after treatment. For these reasons, in the discussions that follow, only elevation of creatinine is considered as evidence of significant azotemia.

### Urinalysis

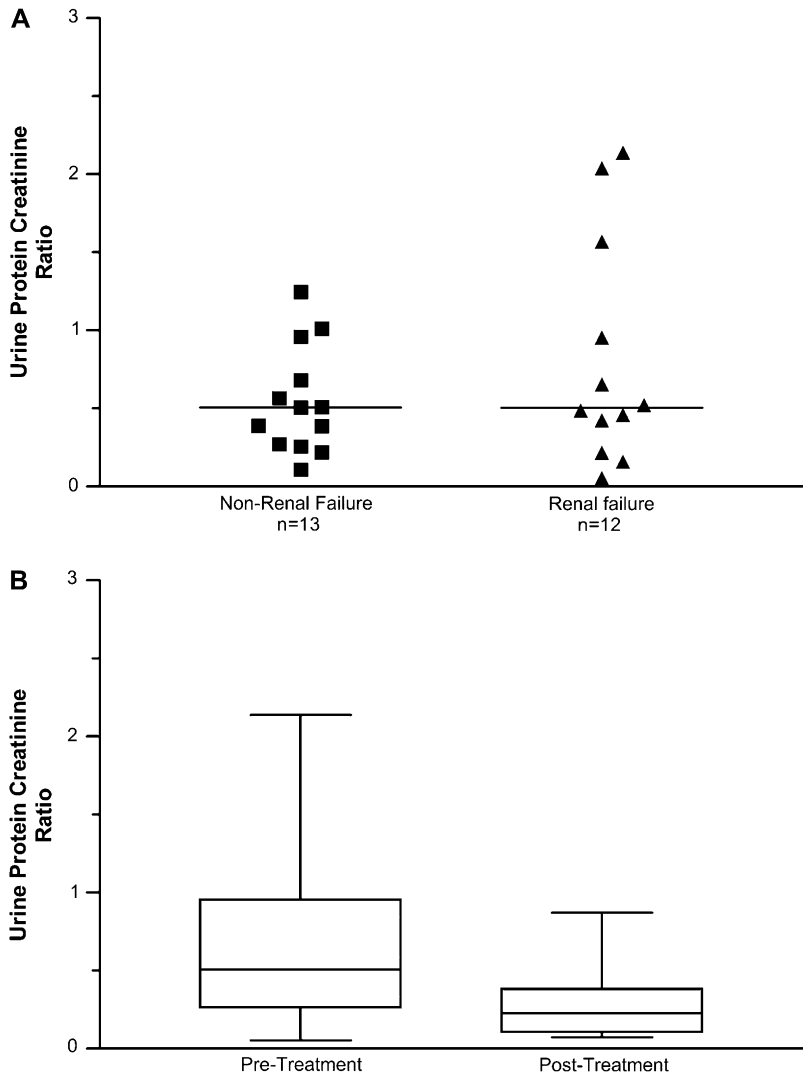
Polyuria or polydipsia was observed in up to 74% of cats with hyperthyroidism in early reports of the condition [36]. The prevalence of these clinical signs is thought to be decreasing as a result of earlier diagnosis of hyperthyroidism [34]. Urine specific gravity does not seem to be strongly correlated with changes in GFR in cats with hyperthyroidism, because a consistent decrease in specific gravity does not occur with treatment [72,75,76]. Thus, it is important to recognize that some hyperthyroid cats are polyuric or polydipsic without having any evidence of renal disease and that this problem may resolve with treatment for hyperthyroidism. It has been suggested that psychogenic polydipsia, possibly caused by heat intolerance, may play a pathogenic role in some cats [77].

In one study, 12% of cats with hyperthyroidism were diagnosed with urinary tract infections, although, interestingly, none of the affected cats was showing any clinical signs of lower urinary tract disease [78]. Because only cats that remained nonazotemic after treatment for hyperthyroidism were included in that study, it is possible that the prevalence of infections might have been even higher had cats with renal compromise been included.

Mild proteinuria is frequently present in cats with hyperthyroidism. The proteinuria tends to resolve with treatment, even in cats that develop azotemia (Fig. 2) [79]. It is thought that the proteinuria is a reflection of the glomerular hypertension and hyperfiltration that is known to occur in the hyperthyroid state. Alternatively, changes in urinary protein excretion may reflect differences in tubular protein handling. Although, as discussed previously, a change in the structure of the glomerular barrier has been proposed as a cause for the proteinuria observed in hyperthyroid animals, the rapid decrease in protein excretion with treatment for hyperthyroidism seems to make this explanation less likely.

### Prediction of Azotemia After Treatment

A significant proportion of cats that are treated for hyperthyroidism become azotemic, but objective data documenting exactly how common this is are lacking. Estimates vary, but in an unselected population of hyperthyroid cats seen in first-opinion clinics in central London, approximately a third become azotemic after treatment [80]. As discussed previously, this is considered to be attributable to the “unmasking” of chronic kidney disease (CKD) in patients with significantly increased GFR attributable to the hemodynamic effects of hyperthyroidism. Even cats that develop azotemia are likely to appear clinically improved after treatment for hyperthyroidism, leading to an underestimation of the proportion of cats that develop azotemia unless renal function is systematically retested in all cats that are treated.



**Fig. 2.** (A) Urine protein creatinine ratios (UPCs) in untreated hyperthyroid cats. There was no difference in the UPCs of cats that developed azotemia (renal failure group) or remained non-azotemic (non-renal failure group) after treatment for hyperthyroidism. A reference range for UPC derived from normal geriatric cats in the same clinic had an upper limit of 0.43. More than half of the hyperthyroid cats in this study had a UPC ratio that exceeded this. (B) There was a significant ( $P < .001$ ) decrease in UPC after treatment ( $n = 19$ ) for hyperthyroidism.

Development of azotemia after treatment for hyperthyroidism can be predicted from pretreatment GFR measurements. In one study, a pretreatment GFR of  $<2.25$  mL/kg/min had 100% sensitivity and 78% specificity for the development of posttreatment azotemia [76]. GFR measurements are not widely

performed in general practice, however, so attempts have been made to predict the development of azotemia from data obtained from the history, physical examination, or routine biochemistry and urinalysis. It is suggested that azotemia is more likely to develop in older patients and in those with small or irregular kidneys [77,80]. Intuitively, higher creatinine concentrations (even when within the laboratory reference range), lower urine specific gravity, and extremely high pretreatment total  $T_4$  concentrations increase the risk of a patient being azotemic after treatment for hyperthyroidism. No single parameter has been shown to be consistently useful in this prediction, however.

Interestingly, although many cats may be mildly azotemic after treatment for hyperthyroidism, it is not clear how clinically significant this finding is. A study comparing the survival of cats that developed azotemia with those that remained nonazotemic after treatment for hyperthyroidism in an unselected population of cats presented to first-opinion practice did not find any difference between the two groups [81]. Median survival time of the cats that developed azotemia was 595 (range: 62–2016) days compared with 584 (range: 29–2044) days for the cats that did not. These survival times are only slightly shorter than those of cats treated with radioactive iodine, of which it is estimated that 30% to 41% have significant renal problems at their time of death [82,83]. Cats that are treated with radioactive iodine are likely to be selected, to some extent, for a favorable response to treatment because of the cost, the requirement for a period of isolation, and the irreversible nature of the treatment.

A recent study reported that the activity of the tubular enzyme *N*-acetyl- $\beta$ -D-glucosaminidase (NAG) was increased in hyperthyroid cats that went on to develop azotemia with treatment compared with hyperthyroid cats that remained nonazotemic [84]. The number of cats included in the study was small, but the result is worthy of further investigation.

### Choice of Treatment Modality

It is generally recommended that hyperthyroidism in cats be initially treated medically for a sufficient period to determine whether significant azotemia is likely to develop with the return to euthyroidism. This approach is prudent and allows the owner of a patient to make an informed decision as to whether or not a more permanent form of treatment (radioactive iodine or surgery) should be undertaken. In light of the information given previously regarding survival times, the author does not discourage owners of cats that are mildly azotemic following medical treatment from treating these cats with radioactive iodine or surgical thyroidectomy, provided that the owners are well informed and the patient is acting clinically well.

Methimazole has antioxidant properties that confer a degree of protection against cisplatin- and gentamicin-induced renal injury in experimental models [85,86]. Because the decline in GFR with treatment for hyperthyroidism is related to hemodynamic changes rather than to nephrotoxicity, however, there is no reason to suppose that treatment with this drug confers an intrinsic benefit

over the other treatment modalities other than its reversibility. Sometimes, cats that are nonazotemic after treatment with methimazole or carbimazole become azotemic when treated by thyroidectomy or with radioactive iodine. This is usually a result of better control of hyperthyroidism with these treatment methods.

In the author's opinion, it is rarely advisable to undertreat hyperthyroidism deliberately in an attempt to maintain renal parameters within the laboratory reference range, because glomerular hyperfiltration may ultimately be detrimental to renal function as discussed elsewhere in this article.

### Treatment of Hyperthyroid Cats That Are Azotemic Before Therapy

Only a small number of hyperthyroid cats are azotemic (have elevated creatinine concentration) before treatment, but these patients can be challenging to diagnose and treat. A retrospective study of cats that had been diagnosed with azotemic CKD and were suspected, and eventually proven, to have concurrent hyperthyroidism found that only 43% had an elevated total  $T_4$  concentration when it was first measured [87]. The diagnosis of hyperthyroidism in the remaining cats was eventually confirmed by repeated measurements of total  $T_4$  or by a  $T_3$  suppression test. The study also found a relatively high rate of false-positive test results using free  $T_4$  measurements and recommended that this test not be used in isolation for the confirmation of hyperthyroidism, a finding that is in accordance with the work of other authors [88,89].

It is important to recognize that diagnosis of cats with concurrent CKD and hyperthyroidism is often not straightforward. Clinical suspicion that hyperthyroidism is present, or is developing, is facilitated by good clinical record keeping. Insidious weight loss in a patient that the owner believes is doing well otherwise and that is maintaining a reasonable appetite in spite of documented CKD should alert the clinician to the possibility of concurrent hyperthyroidism, as should unexplained increases in liver enzyme activities. It is worth noting that creatinine concentration may decrease quite significantly in a patient with renal failure that develops hyperthyroidism; this can be useful in alerting the clinician to the possibility that hyperthyroidism is developing, because there are few clinical conditions that actually cause GFR to increase over time.

When hyperthyroidism is diagnosed in a patient that is concurrently azotemic, medical treatment should be introduced gradually, starting with a low dose of methimazole or carbimazole. This should be increased gradually to the point at which optimum benefit seems to be achieved in terms of general demeanor and weight gain. This is almost inevitably accompanied by worsening azotemia. It is essential to treat the cat and not the numbers in this situation and to recognize that treating hyperthyroidism is likely to result in a decline in GFR (and therefore a worsening of the azotemia) in most patients but that, ultimately, the cat may be best served by controlling the hyperthyroidism. Because the total  $T_4$  concentration is often not elevated before commencing treatment, it can be difficult to know what the therapeutic end point should be. Cats that are azotemic before commencing treatment for hyperthyroidism

have short survival times compared with those that only develop azotemia after treatment; reviewing case records of cats treated at the first-opinion clinics of the Royal Veterinary College shows that the median survival time of 30 cats that were azotemic before commencing treatment was approximately 6 months (median survival = 213 days, range: 8–1617 days) (Jenny Wakeling, unpublished data, 2007). Many published studies have excluded cats that were azotemic before treatment; thus, few objective data are available in this regard.

### Is Hyperthyroidism Damaging to the Feline Kidney?

As discussed previously, a significant number of hyperthyroid cats develop azotemia after treatment. What is not known is whether this proportion of middle-aged and elderly cats would be expected to have CKD or whether CKD is more common in hyperthyroid cats than in the population at large. There are few good estimates of the prevalence of CKD in the feline population. One study found that 15% of cats older than 15 years presented to North American veterinary schools had renal failure, although this figure may not be representative of the feline population as a whole [90]. As a result, it is impossible to reach firm conclusions regarding whether more hyperthyroid cats develop CKD than would be expected. Further epidemiologic studies are required in this area.

Glomerular hypertension has been demonstrated to cause progressive decline in renal function in the rat and has been proposed as a mechanism for intrinsic progression of CKD in the cat. Indirect evidence that glomerular hypertension occurs in hyperthyroid cats is provided by the observation that urinary protein excretion is increased in many cats at diagnosis, but this resolves rapidly with treatment [79]. Proteinuria has been associated with shortened survival times in cats with CKD or systemic hypertension [91] and also in older apparently healthy cats [92]. It is suggested that the proteinuria may be directly injurious to the kidney, because trafficking of protein through the tubulointerstitium in rats has been demonstrated to cause upregulation of various inflammatory mediators and profibrotic cytokines [93]. It is also possible that proteinuria is simply a marker for glomerular hypertension, with the damage being mediated by means of other mechanisms. Alternatively, proteinuria may be a reflection of a particular type of glomerular lesion that is intrinsically more rapidly progressive.

An additional mechanism that could contribute to renal injury in feline hyperthyroidism is hyperparathyroidism. Hyperthyroid cats have frequently been shown to have elevated parathyroid hormone (PTH) concentrations [94]. Hyperparathyroidism can result in calcification of soft tissues, including the kidney, and has been proposed as a mechanism for the intrinsic progression of CKD. Dietary phosphate restriction, which decreases PTH concentration, has been shown to prolong the survival of cats with CKD [95]. The role, if any, of hyperparathyroidism in the development of CKD in cats with hyperthyroidism is an interesting avenue for further study.



## SUMMARY

CO is increased in the hyperthyroid state because of the combined effects of a decrease in SVR and an increase in resting heart rate, resulting in increases in left ventricular ejection fraction and increased blood volume. Cardiovascular manifestations of hyperthyroidism are common in the cat, although the occurrence of overt heart failure is low and seems to be decreasing as the disease is diagnosed earlier in its clinical course. Although CO is increased in hyperthyroidism, the concomitant decrease in SVR means that there is little overall change in systemic arterial pressure.

These hemodynamic alterations, together with activation of the RAS and direct tubular mechanisms, are responsible for marked increases in GFR that occur in the hyperthyroid state. Many cats become azotemic after treatment for hyperthyroidism as preexisting CKD is unmasked. What remains to be conclusively determined is whether the hyperthyroidism is intrinsically damaging to the feline kidney. If it is, this would have profound implications for the treatment of this common endocrine disease.

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