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Testing for Hyperthyroidism in Cats

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F eline hyperthyroidism was first recognized as a distinct clinical entity in 1979. Since then, it has become an extremely important and common disorder of older cats. The clinical syndrome results from excessive circulating concentrations of the active thyroid hormones thyroxine (T_4), and triiodothyronine (T_3) produced by an abnormally functioning thyroid lobe. The underlying pathologic finding in more than 98% of cases is benign adenomatous hyperplasia (adenoma); as such, the disease carries a favorable prognosis with effective therapy. Thyroid carcinoma is a rare cause of hyperthyroidism in cats. Hyperthyroidism has also been described in a young kitten, but this likely represents a separate disease entity that remains extremely rare [1].

The clinical features of feline hyperthyroidism have by now been well described. Because of the multisystemic effects of thyroid hormones, a wide variety of clinical signs are possible; however, today, presumably because of increased awareness and earlier diagnosis, cats are far less symptomatic than previously [2,3]. There has been a change in emphasis from simply confirming a diagnosis in a cat presenting with classic clinical signs to diagnosing hyperthyroidism in cats with few, if any, signs or ruling it out in cats presenting with varied problems that may or may not be related to hyperthyroidism. This has an impact on the efficacy of the diagnostic tests used, because the changes induced by hyperthyroidism become more subtle and the possibility of occult hyperthyroidism with or without a concurrent disease becomes greater. This article reviews those routine clinicopathologic and endocrinologic changes typically associated with hyperthyroidism and highlights recent advances in the diagnostic tests used to support and confirm a diagnosis of hyperthyroidism in cats.

SCREENING LABORATORY TESTS

A complete blood cell count, serum biochemistry, and urinalysis are often performed in the investigation of hyperthyroidism, and such results may prove

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useful in supporting a diagnosis or eliminating other diseases with similar clinical signs.

Hematologic Analyses

In early reports of hyperthyroidism, mild to moderate erythrocytosis and macrocytosis were common. In one study of 131 hyperthyroid cats, an increased packed cell volume (PCV), mean corpuscular volume (MCV), red blood cell (RBC) count, and hemoglobin concentration were reported in 47%, 44%, 21%, and 17% of cases, respectively, and the prevalence of such changes remained as high 10 years later [2,3]. Such changes may reflect increased erythropoietin production resulting from increased oxygen consumption or direct thyroid hormone–mediated β-adrenergic stimulation of erythroid marrow. In a similar study of 57 cats in the United Kingdom, however, there were minimal changes in RBC parameters and macrocytes were rare [4]. Anemia seems to be rare and usually associated with severe hyperthyroidism, and it may result from bone marrow exhaustion or iron or other micronutrient deficiency [4]. A significantly higher incidence of Heinz body formation has been reported in cats with hyperthyroidism compared with healthy cats, although with fewer and smaller bodies than typically seen in diabetic cats [5]. Hyperthyroid cats also seem to have a higher mean platelet size than healthy cats, but the significance of this remains unclear [6].

Changes in white blood cell parameters are not unusual in hyperthyroidism but are relatively nonspecific. The most frequent changes include leukocytosis, mature neutrophilia, lymphopenia, and eosinopenia presumably reflecting a stress response [2–4]. Eosinophilia and lymphocytosis may occur in a small number of cats, however, and potentially result from a relative decrease in available cortisol because of excess circulating thyroid hormone concentrations [4].

It is important to note that apart from the rare cases of thyrotoxic anemia, the hematologic abnormalities are subtle in hyperthyroid cats and are not clinically significant. In some affected cases, hematologic parameters may not be altered, and in hyperthyroid cats with concurrent illness, the abnormalities present may reflect the latter rather than the former disease.

Biochemical Analyses

The most striking biochemical abnormalities are elevations in the liver enzymes, alanine aminotransferase (ALT), alkaline phosphatase (ALKP), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). At least one of these enzymes is elevated in more than 90% of hyperthyroid cats [2–4]. The elevations in these enzymes can be dramatic (>500 IU/L each, respectively), but at least in one study, serum ALKP and total T_4 concentrations were significantly correlated [7]. As such, the degree of elevation is more subtle, if present at all, in early cases of hyperthyroidism. In addition, liver enzyme concentrations decrease to within the reference range with successful management of hyperthyroidism [8]. If marked elevations in liver enzymes are observed in cats with mildly elevated thyroid hormone concentrations or if

such elevations persist despite successful treatment of the hyperthyroidism, concurrent hepatic disease should be considered and investigated.

Despite the marked elevations in hepatic enzymes, histologic examination of the liver of hyperthyroid cats has revealed only modest and nonspecific changes, including increased pigment within hepatocytes, aggregates of mixed inflammatory cells in the portal regions, and focal areas of fatty degeneration [9]. In more severe cases, centrilobular fatty infiltration may occur together with patchy portal fibrosis, lymphocytic infiltration, and proliferation of bile ducts [3,9]. Suggested explanations for such abnormalities have included malnutrition, congestive cardiac failure, infections, hepatic anoxia, and direct toxic effects of thyroid hormones on the liver. Several reports have examined the possibility of other sources of these enzymes, however, and have shown that the liver and bone contribute to increased ALKP activity in hyperthyroid cats [7,10,11]. In one of these studies, the bone isoenzyme contributed up to 80% of the total ALKP activity [10].

Hyperphosphatemia, in the absence of azotemia, was originally reported in approximately 20% of cases and was more recently reported in a higher percentage (36%–43%) of hyperthyroid cats, particularly when compared with an age-matched control group [3,10,12]. This, together with the elevation in the bone isoenzyme of ALKP, is consistent with altered bone metabolism in hyperthyroidism. Certainly, in human thyrotoxic patients, there is an increased risk of osteoporosis because of a direct effect of thyroid hormone on bone. The net bone loss leads to the release of calcium and a tendency toward hypercalcemia, hyperphosphatemia, hypoparathyroidism, and reduced concentrations of activated vitamin D. Studies in hyperthyroid cats have demonstrated significant differences compared with people, however. Circulating osteocalcin concentration, used as a measure of osteoblastic activity and bone remodeling, although variable, was elevated (mean $\pm$ SD: 0.32 $\pm$ 0.3, range: 0–1.7 ng/mL) in 16 (44%) of 36 hyperthyroid cats compared with values from 10 healthy cats (range: 0–0.25 ng/mL) [10]. In a further preliminary study, osteocalcin, the bone isoenzyme of ALKP, the carboxy-terminal propeptide of type I collagen (PICP), the carboxy terminal telopeptide of type I collagen (ICTP), serum cross-linked carboxy-terminal collagen telopeptide (CTx), and deoxypyridinoline (Dpd) concentrations were measured in 4 healthy and hyperthyroid cats before and after radioactive iodine treatment. All concentrations were increased in the hyperthyroid cats and decreased after successful therapy, suggesting thyrotoxic-induced increased bone turnover [13]. Early reports of feline hyperthyroidism suggested that the circulating calcium concentration was largely unaffected by hyperthyroidism, but only total calcium was measured. In two separate studies, 18 (50%) of 36 [10] and 4 (27%) of 15 [12] hyperthyroid cats had serum ionized calcium concentrations lower than the reference range. In addition, hyperparathyroidism seems to be common in hyperthyroid cats [12]. In 30 hyperthyroid cats, the circulating parathyroid hormone (PTH) concentration was elevated in 23 (77%) cases (mean $\pm$ SEM: 85.0 $\pm$ 17.2, range: 33.1–120.3 pg/mL [reference range: 2.9–26.3 pg/mL]), with values approaching up to 19 times the upper

limit of the reference range. Of 8 hyperthyroid cats in which the plasma 1,25 vitamin D concentration was measured, three values were higher than the reference range rather than suppressed as in human beings, but there was no overall significant difference between this group and 20 healthy cats [12]. The etiology of hyperparathyroidism, hyperphosphatemia, ionized hypocalcemia, and elevated bone marker concentrations in cats remains unclear and warrants further study. These abnormalities have not typically been associated with any specific clinical signs. There has been at least one report of a hyperphosphatemic hyperthyroid cat with calcification of multiple paws that resolved with induction of euthyroidism, however [14]. There has also been some suggestion that the altered bone marker concentrations may provide a sensitive method for monitoring treatment in hyperthyroid cats, but further studies are required. Although not typically associated with human hyperthyroidism, concurrent hyperparathyroidism has recently been diagnosed in 13 of 96 patients [15], and the cat may prove to be a suitable model for further investigations in this field.

In early reports of hyperthyroidism, mild to moderate azotemia seemed to be common, occurring in 25% to 70% of cases [3,4]. Current figures suggest that just more than 10% of hyperthyroid cats are azotemic. Although azotemia is not unexpected in a group of aged cats, it could be exacerbated by the increased protein catabolism and prerenal uremia of thyrotoxicosis [9]. Most studies have shown relatively lower pretreatment urea concentrations in hyperthyroid cats [16–20] when compared with posttreatment values, however. This is presumably related to the elevated glomerular filtration rate (GFR) associated with hyperthyroidism, resulting from increased cardiac output and renal afferent arteriolar vasodilation [13,16–18]. In hyperthyroid cats without azotemia, the serum creatinine concentration is significantly lower compared with age-matched healthy animals [12] and significant increases have been documented after treatment [13]. These low values may be related to reduced muscle mass rather than to any effect of thyrotoxicosis on tubular secretion of creatinine, because this is not considered to occur in cats. Together with the effects of hyperthyroidism on urea concentrations, this has significant implications when assessing renal function before deciding on the best option for treatment.

Several other clinicopathologic abnormalities have been described in hyperthyroid cats. Hypokalemia has been reported in up to 17% of hyperthyroid cats, [21] but although the etiology remains unclear, it is rarely clinically significant [22]. In a study of 15 hyperthyroid and 40 healthy cats, there was no significant difference in circulating ionized or total magnesium concentrations between the two groups [23]. This contrasts to other species, in which hyperthyroidism increases magnesium excretion and lowers circulating concentrations. There was a negative correlation between ionized magnesium concentrations and logarithmically transformed total T_4 concentrations in the hyperthyroid group, however, suggesting some correlation with lowered magnesium concentration and the severity of the hyperthyroid state.

Blood glucose concentrations may be elevated in hyperthyroid cats, presumably reflecting a stress response [3]. Hyperthyroidism is also associated with

glucose intolerance characterized by delayed clearance of administered glucose from the plasma despite increased secretion of insulin [24]. Two separate studies have examined the effect of hyperthyroidism on circulating fructosamine concentration [25,26]. In both studies, the serum fructosamine concentration was significantly lower in hyperthyroid cats compared with healthy cats, presumably as a result of increased protein turnover. Importantly, 17% to 50% of cases had values lower than the respective reference range, and caution is advised in interpreting the serum fructosamine concentration in hyperthyroid cats, particularly if they are concurrently diabetic. Almost 50% of hyperthyroid cats have detectable serum troponin I concentrations, with a marked reduction in this percentage after therapy, consistent with hyperthyroid-induced myocyte damage [27]. Abnormal coagulation parameters were detected in 3 of 21 cats before methimazole therapy [28]. All 3 cats had elevated proteins induced by vitamin K absence or antagonism; 1 cat also had an elevated prothrombin time. This could be attributable to the reduced fat absorption seen in some hyperthyroid cats [3] or to concurrent small intestinal disease. A separate study reported serum folate and cobalamin concentrations lower than the reference range in 5 (38.5%) and 3 (23.1%) of 13 hyperthyroid cats, respectively [29]. The cause warrants further investigation but may be associated with malabsorption or increased metabolism.

Other biochemical parameters, such as cholesterol, sodium, chloride, bilirubin, albumin, and globulin, are rarely, if ever, affected by hyperthyroidism. Of all the possible biochemical abnormalities, elevated liver enzyme activities remain the change most commonly associated with hyperthyroidism. The other reported changes are variably associated with hyperthyroidism and provide little diagnostic information.

Urinalysis

Routine urinalysis in thyrotoxic cats seems to be noncontributory. Urine specific gravity values are extremely variable and ranged from 1.009 to 1.050 (mean = 1.031) in 57 hyperthyroid cats, with only two values (4%) less than 1.015 [3]. This was not significantly different when compared with values obtained from hyperthyroid cats 10 years later [2].

Proteinuria is common in hyperthyroid cats. In one study, the urinary protein/creatinine ratio (UPC) was elevated (>0.5) in 15 (34%) of 44 hyperthyroid cats that were nonazotemic and had no evidence of a urinary tract infection [30]. In the same study, 27 cats (61%) had a urinary albumin/creatinine ratio (UAC) greater than 30 mg/g, with 18% having a ratio greater than 82 mg/g, which are cutoff points representing established limits for albumin excretion. The severity of the proteinuria decreased in most cats after treatment. Neither an elevated UPC nor an elevated UAC was predictive of the development of renal failure, and their pathogenic significance remains unclear.

Urinary corticoid/creatinine ratios are significantly higher in untreated hyperthyroid cats, with 15 (47%) of 32 cats having concentrations greater than the upper limit of the reference range (42.0×10^{-6}) [31]. In these cats, values

reached up to four times this upper limit and presumably reflect increased metabolic clearance of cortisol and activation of the hypothalamic-pituitary-adrenal axis by the disease. Therefore, elevated urinary corticoid/creatinine ratios should be interpreted with caution, and hyperthyroidism should be ruled out if hyperadrenocorticism is being considered.

DEFINITIVE DIAGNOSTIC TESTS

The diagnosis of hyperthyroidism is confirmed by the demonstration of increased thyroidal radioisotope uptake or circulating concentrations of the thyroid hormones.

Thyroidal Radioisotope Uptake

Uptake of radioactive iodine isotopes (^{131}I or ^{123}I) and technetium Tc 99m as pertechnetate ([99m]Tc0$_4^-$) is increased in hyperthyroid cats [3,32–35]. The radioactive iodine isotopes and pertechnetate are trapped and concentrated within the thyroid gland. Unlike ^{131}I and ^{123}I, however, pertechnetate is not organically bound to thyroglobulin or stored within the thyroid gland. The relatively long half-life, higher γ-energy, and β-emission of ^{131}I and the higher expense of ^{123}I make their routine use in feline thyroid scintigraphy uncommon. Because of availability, lower cost, and superior image quality, pertechnetate is preferred.

Percentage thyroid uptake of pertechnetate is routinely measured between 20 and 60 minutes after intravenous injection [32,33]. Values are significantly higher in hyperthyroid cats compared with healthy cats and correlate well with circulating thyroid hormone concentrations [36]. Calculation of the percentage uptake of pertechnetate is not routinely performed, however, because it requires accurate assessment of the injected dose together with correction for background radioactivity. Similar if not more diagnostically efficient results are obtained if the thyroid/salivary (T/S) ratio is calculated, and this provides the best correlation with serum total T_4 concentrations [36]. It is generally accepted that the T/S ratio in healthy cats is <1 [36], although values as high as 1.66 have been reported [37], indicating the need for validation in individual centers. For assessment of the T/S ratio, pertechnetate may be administered subcutaneously or intravenously [38].

It is clear that quantitative thyroid imaging is not required for the diagnosis of hyperthyroidism in most cats. Theoretically, however, it could provide important diagnostic information in some cats. Nonthyroidal illness likely exerts less effect on the results of scintigraphy than basal total T_4 concentration and could potentially exclude hyperthyroidism in those few euthyroid cats with an elevated free T_4 concentration. In addition, results of scintigraphy may be abnormal in cats with early hyperthyroidism and reference range circulating thyroid hormone concentrations. In a preliminary study of 6 occult hyperthyroid cats, the diagnostic value of pertechnetate scans was considered greater than that of thyroid hormone measurements [39]. In a further study of 23 cats with palpable thyroid nodules and reference range circulating total T_4 values,

16 were diagnosed as hyperthyroid on the basis of scintigraphy (T/S ratio >1), and these cats had, as a group, significantly higher serum free T_4 concentrations than those with a normal T/S ratio [40].

Thyroid scintigraphy is expensive, requiring access to sophisticated equipment, and is not without limitations as a diagnostic tool. One study demonstrated positive scintigraphy results in 14 cats in which there was a clinical suspicion of hyperthyroidism but reference range serum total T_4 concentrations [41]. Three of these cats exhibited >60% T_4 stimulation after administration of thyrotropin-releasing hormone (TRH), however, and, subsequently, no histopathologic evidence of thyroid disease was found. Therefore, the specificity of thyroid scintigraphy warrants further investigation.

Methimazole administration may also affect scintigraphy findings. Methimazole and other related drugs inhibit the thyroid peroxidase enzyme, reducing organification of iodine and inhibiting coupling of iodotyrosines. Although methimazole exerts no direct effect on thyroidal iodide uptake, a reduction in T_4 and a consequent elevation in the thyroid-stimulating hormone (TSH) concentration are potentially associated with increased iodide uptake. One study of five healthy cats showed a significant increase in the percentage uptake of pertechnetate and the T/S ratio at 20 minutes after 3 weeks of methimazole therapy to maximal T_4 suppression, from a mean of 0.23% to 1.05% and 0.81 to 1.36, respectively [42]. A similar study in 19 hyperthyroid cats showed no significant change in either of these parameters after a minimum of 30 days of methimazole therapy [43]. At that time, all cats had total T_4 concentrations less than 51.5 nmol/L but circulating TSH concentrations remained suppressed, suggesting that the mechanism of increased trapping had not yet been activated. Two of the cats with unilateral disease seemed to have bilateral disease after treatment, possibly reflecting increased thyroidal radioisotope uptake, and in these cats, this diagnosis was supported by the greatest increase in TSH concentrations. Therefore, recent administration of methimazole must be considered during quantitative interpretation of thyroid scintigraphy.

Radioactive iodine is also affected by methimazole therapy, with mean 8-hour uptake values representing iodide trapping, increasing from a mean of 2.1% to 4.1% after 3 weeks of therapy [42]. Interestingly, the 24-hour uptake in this same group fell from a mean of 7.04% to 5.16%, presumably reflecting methimazole-induced reduction in organification and coupling within the thyroid gland. Withdrawal of methimazole was associated with markedly increased 8- and 24-hour uptake values peaking between 4 and 9 days after cessation of therapy and continuing out to 24 days after withdrawal. This supports a short-term rebound effect that may enhance the efficacy of radioactive iodine therapy but has implications when used as a diagnostic test in cats previously treated with methimazole.

Qualitative scintigraphic imaging, conversely, remains a useful procedure in hyperthyroid cats to determine unilateral or bilateral involvement, alterations in the position of thyroid lobes, the site of hyperfunctioning accessory or ectopic thyroid tissue, or distant metastases from a functioning thyroid carcinoma

[44]. Care must be taken in qualitative assessment of lobe involvement in cats previously treated with methimazole, however [43].

## Circulating Thyroid Hormone Concentrations

The elevated circulating thyroid hormone concentration remains the biochemical hallmark of hyperthyroidism. Several reports have evaluated the efficacy of total T_4, total T_3, and free T_4 in confirming a diagnosis of hyperthyroidism. Measurement of TSH, although frequently used in people and long awaited in cats, has not been fully evaluated in the diagnosis of feline hyperthyroidism, because a species-specific assay is not yet available.

Basal total thyroid hormone concentration

The basal total T_4 concentration is greater than the reference range in most hyperthyroid cats [3,4,45]. Serum total T_3 values are often concurrently elevated [3,4,45]. Serum total T_3 values are within the reference range in a significant proportion of hyperthyroid cats; however, 4 (3%) of 131 cats [3], 11 (9%) of 122 cats [4], and, more recently, 59 (29%) of 202 cats [2] had a significantly higher percentage than previously described. In the largest study of 917 hyperthyroid cats thus far studied, the serum total T_3 concentration was within the reference range in 307 (33.5%) cases, representing 163 (79.5%) of 205 cats categorized as mildly hyperthyroid with a serum total T_4 concentration less than 65 nmol/L (Fig. 1) [45]. In most other cases, the total T_4 concentration is usually less than 100 nmol/L, and it is likely that the serum total T_3 concentration would increase into the thyrotoxic range if the disorder were allowed to progress untreated. Severe concurrent nonthyroidal illness may play a role in suppressing the T_3 concentration by inhibiting peripheral conversion of T_4 to T_3, as it does in people, although this seems to be a less common phenomenon in cats [4]. It is becoming increasingly recognized that the serum total T_4 concentration may also be within the middle to high end of the reference range (>30 nmol/L) in a significant percentage (up to and exceeding 10%) of hyperthyroid cats, presumably because of earlier diagnosis or sampling a group of mildly affected animals that would not have been tested previously (Fig. 2) [2,45].

Nonspecific fluctuation of thyroid hormones may account for the reference range total T_4 and T_3 values found in hyperthyroid cats. In one study of 14 mildly affected cats, serum total T_4 and total T_3 concentrations were measured hourly for 10 hours and daily for 15 days in 7 of the cats [46]. In both time frames, serum thyroid hormone concentrations fluctuated to a degree exceeding normal assay variation, with greater fluctuation occurring over the 15-day rather than the 10-hour sampling period. Provided that basal thyroid hormone concentrations are only mildly elevated, the degree of fluctuation can result in reference range values. Increased thyroidal production could result in an increased circulating concentration, but because the serum half-life of thyroid hormones is measured in hours, acute decreases presumably reflect fluctuations in binding proteins or other unclear hemodynamic changes. In cats with markedly elevated serum thyroid hormone concentrations, the degree of fluctuation is of little diagnostic significance [46,47].
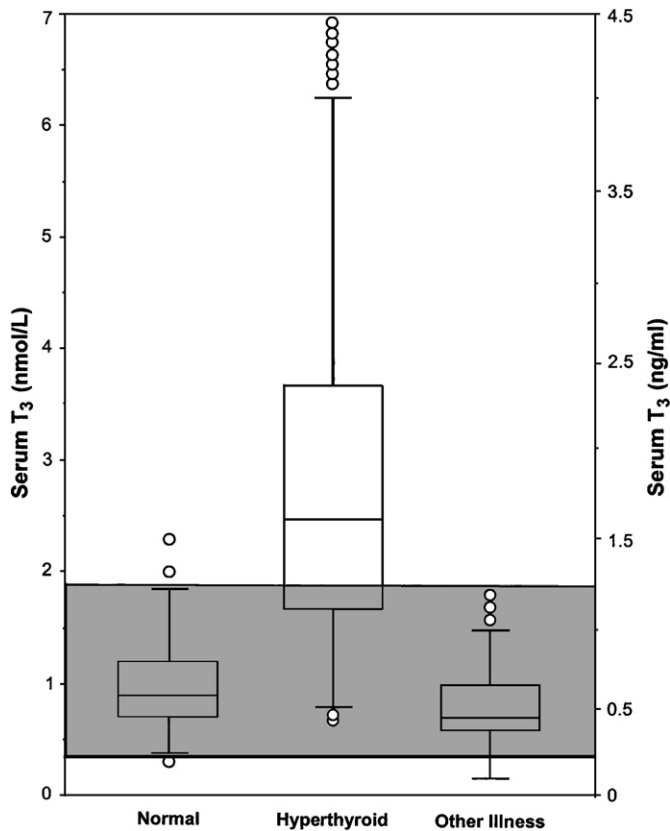
Fig. 1. Box plots of serum T_3 concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). The box represents the interquartile range (25th–75th percentile range or the middle half of the data). The horizontal bar in the box represents the median value. For each box plot, the T-bars represent the main body of data, which is equal to the range in most instances. Outlying data points are represented by open circles. The shaded area indicates the reference range for the serum T_3 concentration. (*From* Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:531; with permission).

The presence of concurrent nonthyroidal illness can also affect the circulating total T_4 concentration in hyperthyroid cats. In 494 cats with a variety of nonthyroidal illnesses, 63 had a palpable thyroid nodule and a significantly higher mean (±SD) serum total T_4 concentration of 21.7 (±10.4) nmol/L than the concentration of 12.7 (±8.1) nmol/L in the cats without a palpable thyroid nodule [48]. Subsequently, the serum total T_4 concentration increased into the thyrotoxic range in 4 of these cats, and adenomatous hyperplasia of the thyroid glands was found at necropsy in 2 other cats. In another study of 110 hyperthyroid cats, 39 had a concurrent nonthyroidal illness [49]. These cats
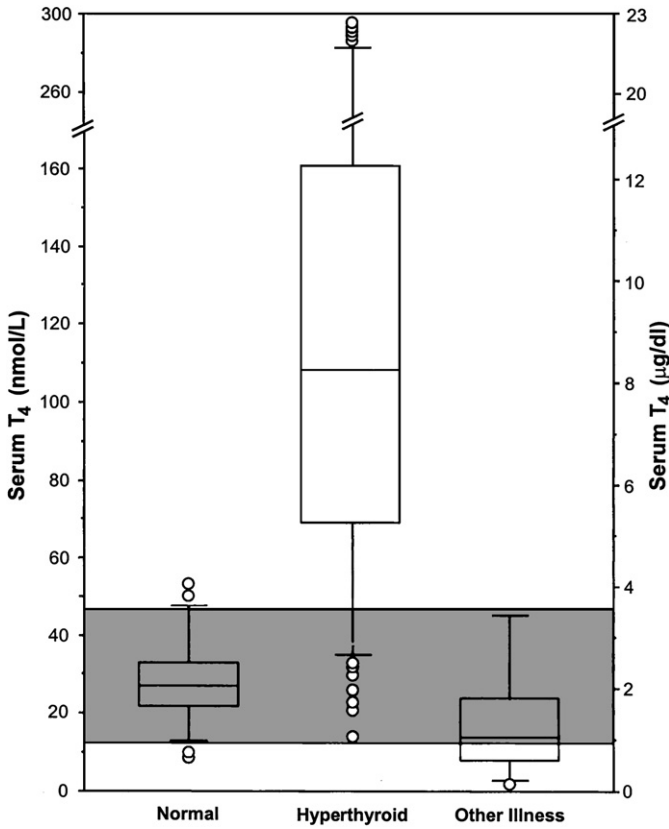
Fig. 2. Box plots of serum total T4 concentrations from 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). See Fig. 1 for key. (*From* Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:531; with permission.)

had a significantly lower serum total T4 concentration than the hyperthyroid cats without a concurrent illness. In total, a reference range serum total T4 concentration was found in 14 (13%) cats, but this only represented 3 (4%) of 71 cats without concurrent disease compared with 11 (28%) of 39 cats with such disorders. In a larger study of 917 hyperthyroid cats, a concurrent illness was identified in 17 (22%) of 80 cats with mild hyperthyroidism and a reference range serum total T4 concentration [45]. In 12 of these cats, the serum total T4 concentration was within the middle to high end of the reference range (>30 nmol/L), whereas values were within the middle to low end of the reference range in the remaining 5 cats, but these had the most severe concurrent illnesses. The mechanisms remain unclear but are more likely to involve changes in protein binding or metabolism rather than any effect on the

hypothalamic-pituitary-thyroid axis [8,48]. Reference range values resulting from the suppressive effect of nonthyroidal disease are only expected in cats with early or mild hyperthyroidism, because the degree of suppression has little diagnostic significance in hyperthyroid cats with a markedly elevated serum total T_4 concentration [4,48,49]. Despite the possibility of encountering middle to high reference range values in mildly hyperthyroid cats with concurrent disease, they usually do not pose a diagnostic dilemma, because serum total T_4 concentrations also decline in euthyroid individuals with similar illnesses [45,48,50]. In euthyroid cats, the degree of suppression is correlated with the severity rather than with the type of illness and can be used as a prognostic indicator (Figs. 3 and 4) [45,48,50]. Low total T_4 values are only expected in
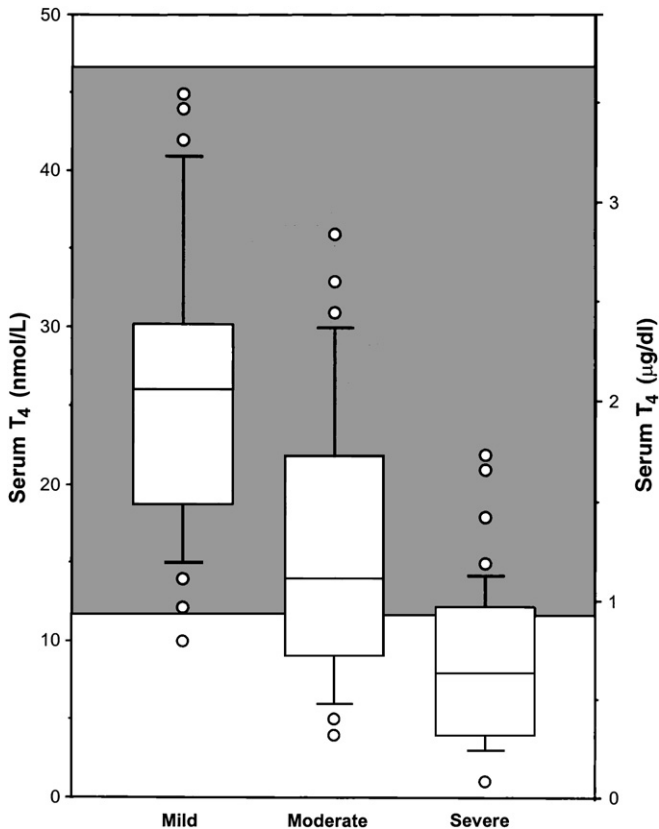
Fig. 3. Box plots of serum total T_4 concentrations from 221 cats with nonthyroidal disease, grouped according to severity of illness. Of the 221 cats, 65 had mild disease, 83 had moderate disease, and 73 had severe disease. See Fig. 1 for key. (*From* Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:533; with permission.)
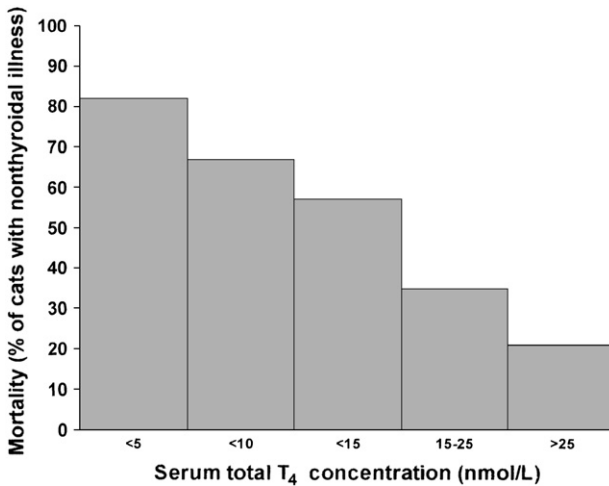
Fig. 4. Relation between mortality and serum total T_4 concentration in 98 cats with nonthyroidal illness. (*From* Mooney CT, Little CJ, Macrae AW. Effect of illness not associated with the thyroid gland on serum total and free thyroxine concentrations in cats. J Am Vet Med Assoc 1996;208:2005; with permission.)

hyperthyroid cats with the most severe concurrent disorders, and in these cases, other criteria, particularly detection of a palpable thyroid nodule, may indicate the need to investigate hyperthyroidism further [45].

Despite the number of drugs that are known to affect circulating thyroid hormone concentrations in people and dogs, there are few reports concerning such an effect in hyperthyroid cats. In eight hyperthyroid cats treated with an immunosuppressive dose of prednisolone administered intramuscularly, there was no significant decrease in the serum total T_4 concentration when assessed 24 hours later [51]. The effects of other drugs have not yet been evaluated.
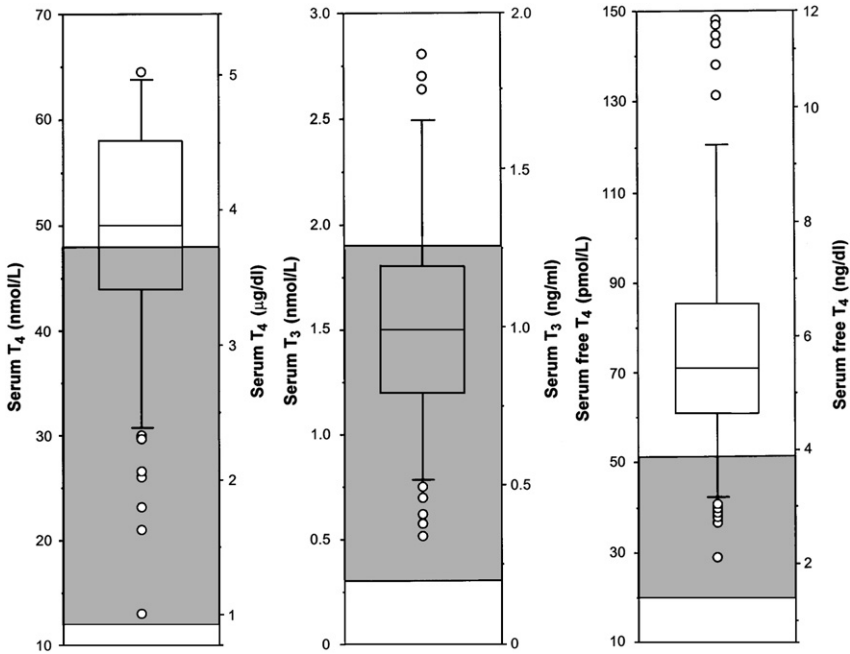
Free thyroxine concentration
In human thyrotoxicosis, assessment of free T_4 is considered a better diagnostic test for hyperthyroidism because it is less affected by nonthyroidal factors than is total T_4 and provides a more accurate reflection of thyroid status. Notably, when the serum total T_4 concentration is increased, the concentration of free T_4 is disproportionately increased, and this may be related, in part, to relative saturation of binding proteins by T_4 and a subnormal concentration of the primary binding proteins. In addition, the serum free T_4 concentration remains elevated in hyperthyroid patients with nonthyroidal illnesses when the total T_4 concentration is suppressed into the reference range. Measurement of the free T_4 concentration has recently been evaluated in hyperthyroid cats and seems to be a useful diagnostic test, particularly in cats with a reference range serum total T_4 concentration (Fig. 5) [45]. The serum free T_4 concentration was elevated in 903 (98.5%) of 917 hyperthyroid cats, whereas the
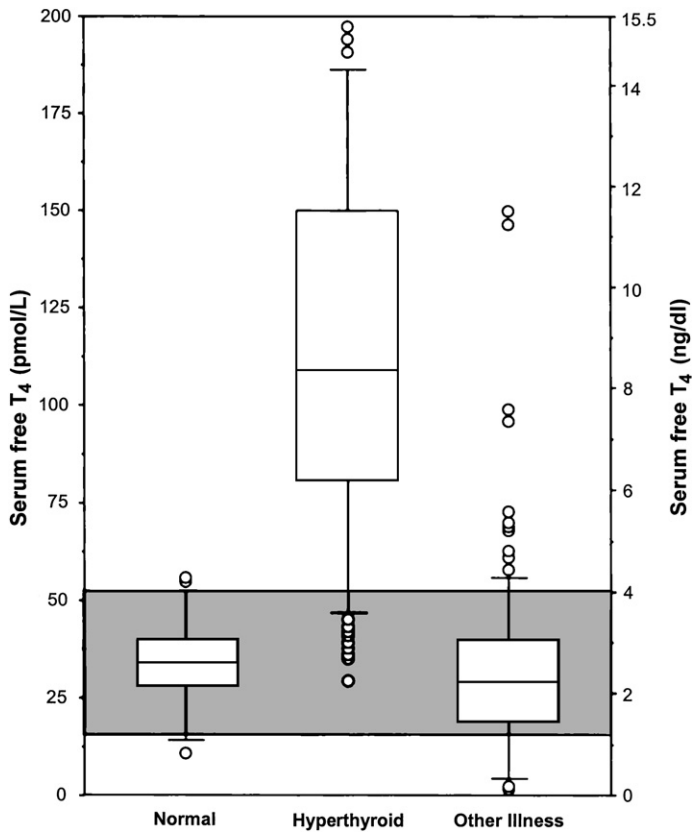
Fig. 5. Box plots of serum free T_4 concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). See Fig. 1 for key. (*From* Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:532; with permission.)

corresponding serum total T_4 concentration was elevated in 837 (91.3%) cases. In all cats with a markedly elevated serum total T_4 concentration, the free T_4 concentration was concurrently elevated, adding little diagnostic information to that already obtained. In 205 of these cats categorized as mildly hyperthyroid with or without a concurrent illness, however, the serum free and total T_4 concentrations were elevated in 191 (93.2%) and 125 (61%) cases, respectively (Fig. 6). The increased diagnostic sensitivity of free T_4 measurement is complicated by a loss of specificity, because 6% to 12% of sick euthyroid cats have elevated concentrations [45,50]. The specificity of free T_4 measurement may be substantially lower in certain disease states. In one study comparing free T_4 concentrations in cats with chronic renal failure and hyperthyroidism (n = 16) and hyperthyroidism alone (n = 16), free T_4 concentrations were

Fig. 6. Box plots of serum total T_4, T_3, and free T_4 concentrations in 205 cats with mild hyperthyroidism (defined as total T_4 concentration <66 nmol/L). See Fig. 1 for key. (*From* Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:533; with permission.)

falsely elevated in 31% of the euthyroid cats [52]. The serum free T_4 concentration should therefore be interpreted with caution if used as the sole diagnostic criterion for confirmation of hyperthyroidism. More reliable information is obtained when it is interpreted together with the serum total T_4 concentration. A middle to high reference range total T_4 concentration and an elevated free T_4 concentration are consistent with hyperthyroidism [45]. By contrast, a low total T_4 value and elevated free T_4 value are usually associated with nonthyroidal illness [45,50].

Feline thyroid-stimulating hormone

In human beings, measurement of the circulating TSH concentration is generally used as a first-line discriminatory test of thyroid function. Commercially available assays are second or third generation, with a functional sensitivity up to 30 times lower than the lower limit of the reference range. In addition, there is a log-linear negative feedback relation between free T_4 and TSH, such that marked changes in TSH concentration can be induced by relatively small changes in free T_4. To date, a feline-specific TSH assay has not been

developed commercially, and most studies have focused on using assays designed for canine or human use.

One study has investigated the use of a TSH assay developed for use in dogs for diagnosing hyperthyroidism in cats [53]. The serum TSH concentration was measured in a group of 17 cats with chronic renal failure alone and in 17 cats with hyperthyroidism and renal failure. All the hyperthyroid cats had TSH concentrations at or lower than the lower limit of detection of the canine assay (0.03 ng/mL), whereas 15 of the cats with chronic renal failure had detectable TSH concentrations, with a median of 0.05 ng/mL. Thus, although canine TSH values are statistically lower in hyperthyroid cats compared with euthyroid cats, the assay, because of its relatively high sensitivity, is not helpful in confirming hyperthyroidism in individual cats. Its only value may be in eliminating hyperthyroidism in cats with readily detectable concentrations.

A separate study compared 12 euthyroid cats and 22 hyperthyroid cats using an assay developed for measuring human TSH concentration [54]. The median circulating TSH concentration of 0.14 mIU/L in euthyroid cats was higher than that of 0 mIU/L in hyperthyroid cats. The validity of measuring feline TSH using a human assay is currently unknown, however.

Recently, feline TSH has been expressed and purified in vitro, allowing future development to standardize and improve clinical assays for feline TSH. The development of such an assay would also be invaluable in studies of the pathogenesis of this disorder in cats [55,56].

Dynamic Thyroid Function Tests

Because of the possibility of finding reference range serum thyroid hormone concentrations in hyperthyroid cats, several additional diagnostic tests have been suggested to be useful in confirming a diagnosis (Table 1). In most cases, however, the serum total T_4 concentration increases into the thyrotoxic range if retested several weeks later, obviating the need for further diagnostic tests. Such tests may be required in some cats with clinical signs suggestive of hyperthyroidism, however, when a repeated serum total T_4 concentration remains equivocal and a serum free T_4 measurement is unavailable or unhelpful.

Thyroid-stimulating hormone response test

In an early study, it was suggested that the TSH response test, utilizing bovine TSH, was useful in confirming a diagnosis of hyperthyroidism [3]. In 11 hyperthyroid cats, the mean serum post-TSH total T_4 concentration of 144.1 nmol/L was not significantly different from the mean basal concentration of 127.4 nmol/L, suggesting that the thyroid glands in these cats secrete thyroid hormones independently of TSH control or are producing T_4 at a maximal rate with minimal reserve capacity. Nevertheless, in a larger study of 40 hyperthyroid cats, although the overall limited T_4 response to TSH stimulation was confirmed, it was shown that hyperthyroid cats with equivocal basal total T_4 concentrations exhibit a response indistinguishable from that in healthy cats [57]. The negative correlation between the relative increment and the baseline total T_4 suggests that the abnormal thyroid glands do retain the ability to

Table 1
Dynamic thyroid function tests in cats

	T_3 suppression	TSH response test		TRH response test
Drug	Liothyronine	Bovine TSH	Human TSH	TRH
Dose	15–25 µg every 8 hours for 7 doses	0.5 IU/kg	0.025–0.2 mg per cat	0.1 mg/kg
Route	Oral	Intravenous	Intravenous	Intravenous
Sampling times	0 and 2–4 hours after last dose	0 and 6 hours	1 and 6–8 hours	0 and 4 hours
Assay	Total T_4 (and total T_3 to check compliance/ absorption)	Total T_4	Total T_4	Total T_4
Interpretation				
Euthyroidism	<20 nmol/L with >50% suppression	100% increase	100% increase	>60% increase
Hyperthyroidism	>20 nmol/L ± <35% suppression	Minimal/no increase	Not determined	<50% increase

Abbreviations: T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

respond to TSH but are producing T_4 at maximal rates. Presumably, hyperthyroid cats with the lowest basal total T_4 concentrations have the greatest potential to respond to TSH, although it has been suggested that this response may be related to stimulation of normal thyroid tissue often found within hyperplastic glands [57]. Measurement of the serum total T_3 concentration adds little diagnostic information because of the more variable response found in healthy and hyperthyroid individuals.

Bovine TSH is no longer available as a pharmaceutic preparation. A recent study evaluating the use of recombinant human TSH (rhTSH) for this test in seven euthyroid cats suggested that this was a safe alternative capable of inducing similar T_4 stimulation [58]. Concurrent measurement of free T_4 was also evaluated but added little additional information. Given the expense of rhTSH, this test has limitations in the evaluation of hyperthyroidism in cats.

Thyrotropin-releasing hormone response test
There is a limited total T_4 response to TRH stimulation in hyperthyroid cats. In one study, there was a significant increase in the mean serum total T_4 concentration after TRH administration in 31 healthy cats, 35 mild to moderate hyperthyroid cats, and 15 cats with nonthyroidal illnesses [59]. The percentage increase in total T_4 was considerably less in the hyperthyroid cats compared

with healthy cats and those with other diseases, however. From the results of this study, it was suggested that a relative increase in total T_4 of less than 50% is consistent with mild hyperthyroidism, a value greater than 60% is suggestive of euthyroidism, and values between 50% and 60% remain equivocal. Discriminant analysis, taking into account the basal and absolute difference between basal and post-TRH total T_4 concentrations, can also be used to distinguish hyperthyroidism from euthyroidism. Similar to the TSH response test, measurement of the total T_3 concentration was considered unhelpful because of the greater variability in response within and between groups. A recent study evaluated the ability of the TRH response test to differentiate between hyperthyroid and severely sick euthyroid cats [60]. Of the 36 critically ill cats reported, 22 had clinical and histopathologic evidence of hyperthyroidism, whereas hyperthyroidism was not suspected in the remaining 14 animals. Of these 14 euthyroid cats, 6 had serum total T_4 increases less than 50% of baseline, 2 had increases between 50% and 60%, and 6 had increases greater than 60% after TRH administration. Although 18 of the hyperthyroid cats had a total T_4 increase less than 50% of baseline, 2 had increases between 50% and 60% and 2 had increases greater than 60%. The authors concluded that it was not possible to use this test to differentiate between hyperthyroid cats and those with severe nonthyroidal illness. Adverse reactions to TRH administration seem to be common and include vomiting, excessive salivation, tachypnea, and defecation. These reactions are transient, develop within a few minutes of TRH administration, and usually resolve by the end of the 4-hour test.

Triiodothyronine suppression test
The T_3 suppression test relies on the ability of administered liothyronine, through negative feedback, to decrease T_4 production by the thyroid gland. In hyperthyroidism, because excess circulating thyroid hormone concentrations have already suppressed TSH production and secretion, additional T_3 has minimal effect on T_4 production. Therefore, the serum total T_4 concentration remains significantly higher after liothyronine administration in hyperthyroid compared with euthyroid (healthy and sick) cats, and the percentage decrease is consequently significantly lower [61,62]. Although individual laboratories vary, as a general guideline, the postliothyronine serum total T_4 concentration tends to be greater than 20 nmol/L in hyperthyroid cats and less than 20 nmol/L in euthyroid cats. There is a greater overlap of results in hyperthyroid and euthyroid cats when the percentage change in total T_4 is calculated. Nevertheless, suppression of 50% or more is consistent with euthyroidism, whereas hyperthyroid cats rarely have values exceeding 35%. Discriminant analysis can also be applied to the results to identify those variables providing the best diagnostic sensitivity and specificity, but the overall performance of the test tends to be unaffected [62,63]. Although the T_3 suppression test is capable of diagnosing hyperthyroidism, some authors suggest that it is most useful in confirming euthyroidism and ruling out hyperthyroidism [61]. Unlike the TRH response test, it is not associated with any adverse reactions. It is a relatively prolonged

test, however, and highly depends on good owner compliance in reliably administering liothyronine tablets and adequate gastrointestinal absorption, necessitating confirmation by before and after serum total T_3 measurement [61,63].

ADDITIONAL DIAGNOSTIC TESTS

Ultrasonography has been used to document the dimensions and volume of the thyroid glands in euthyroid and hyperthyroid cats [64]. Mean dimensions of 20.4 mm $\times$ 2.5 mm $\times$ 3.2 mm and 21.1 mm $\times$ 6.7 mm $\times$ 6.8 mm (length $\times$ width $\times$ height) and lobar volumes of 85 mm^3 and 578 mm^3 were recorded in euthyroid and hyperthyroid cats, respectively. Eight of the 16 hyperthyroid cats had unilateral disease, which may have affected results in these cases. Ultrasonography had 85.7% agreement with scintigraphy in defining normal and abnormal thyroid lobes. Thyroid ultrasonography is technically demanding and likely to be operator dependent, however.

A more recent study used helical CT to determine the dimensions and volume of thyroid tissue in clinically healthy cats [65]. The mean thyroid dimensions were 16.5 mm $\times$ 2.0 mm $\times$ 4.31 mm (length $\times$ width $\times$ height) as determined by transverse images, and the mean lobar volume measured 113.75 mm^3. The value of such imaging in the diagnosis of hyperthyroidism remains undocumented. The cost and availability of such technically demanding imaging techniques make their wide use unlikely, however.

SUMMARY

Hyperthyroidism remains a common endocrine disorder of cats. Although relatively easy to diagnose in classically presenting cats, the increased frequency of testing cats with early or mild disease has had significant implications for the diagnostic performance of many of the routine tests currently used. Further advances in the etiopathogenesis and earlier diagnosis are only likely with the advent of a species-specific feline TSH assay.

References

[1] Gordon JM, Ehrhart EJ, Sisson DD, et al. Juvenile hyperthyroidism in a cat. J Am Anim Hosp Assoc 2003;39:67–71.

[2] Broussard JD, Peterson ME, Fox PR. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. J Am Vet Med Assoc 1995;206:302–5.

[3] Peterson ME, Kintzer PP, Cavanagh PG, et al. Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc 1983;183:103–10.

[4] Thoday KL, Mooney CT. Historical, clinical and laboratory features of 126 hyperthyroid cats. Vet Rec 1992;131:257–64.

[5] Christopher MM. Relation of endogenous Heinz bodies to disease and anemia in cats: 120 cases (1978–1987). J Am Vet Med Assoc 1989;194:1089–95.

[6] Sullivan P, Gompf R, Schmeitzel L, et al. Altered platelet indices in dogs with hypothyroidism and cats with hyperthyroidism. Am J Vet Res 1993;54:2004–9.

[7] Foster DJ, Thoday KL. Tissue sources of serum alkaline phosphatase in 34 hyperthyroid cats: a qualitative and quantitative study. Res Vet Sci 2000;68:89–94.

[8] Mooney C, Thoday KL, Doxey DL. Carbimazole therapy of feline hyperthyroidism. J Small Anim Pract 1992;33:228–35.

 [9] Feldman EC, Nelson RW. Feline hyperthyroidism (thyrotoxicosis). In: Feldman EC, Nelson RW, editors. Canine and feline endocrinology and reproduction. St. Louis (MO): Saunders; 2004. p. 152–218.

[10] Archer FJ, Taylor SM. Alkaline phosphatase bone isoenzyme and osteocalcin in the serum of hyperthyroid cats. Can Vet J 1996;37:735–9.

[11] Horney BS, Farmer AJ, Honor DJ, et al. Agarose gel electrophoresis of alkaline phosphatase isoenzymes in the serum of hyperthyroid cats. Vet Clin Pathol 1994;23:98–102.

[12] Barber PJ, Elliott J. Study of calcium homeostasis in feline hyperthyroidism. J Small Anim Pract 1996;37:575–82.

[13] Slater LA, Jackson B, Stevens KB, et al. Evaluation of bone cell activity in four hyperthyroid cats before and after treatment with iodine-131 [abstract]. Presented at the Proceedings of the British Small Animal Veterinary Association. Birmingham (UK), April 1–4, 2004. p. 522.

[14] Declercq J, Bhatti S. Calcinosis involving multiple paws in a cat with chronic renal failure and in a cat with hyperthyroidism. Vet Dermatol 2005;16:74–8.

[15] Abboud B, Sleilaty G, Mansour E, et al. Prevalence and risk factors for primary hyperparathyroidism in hyperthyroid patients. Head Neck 2006;28:420–6.

[16] Adams WH, Daniel GB, Legendre AM. Investigation of the effects of hyperthyroidism on renal function in the cat. Can J Vet Res 1997;61:53–6.

[17] Adams WH, Daniel GB, Legendre AM, et al. Changes in renal function in cats following treatment of hyperthyroidism using ^{131}I. Vet Radiol Ultrasound 1997;38:231–8.

[18] Becker TJ, Graves TK, Kruger JM, et al. Effects of methimazole on renal function in cats with hyperthyroidism. J Am Anim Hosp Assoc 2000;36:215–23.

[19] DiBartola SP, Broome MR, Stein BS, et al. Effect of treatment of hyperthyroidism on renal function in cats. J Am Vet Med Assoc 1996;208:875–8.

[20] Graves TK, Olivier NB, Nachreiner RF, et al. Changes in renal function associated with treatment of hyperthyroidism in cats. Am J Vet Res 1994;55:1745–9.

[21] Milner RJ, Channell CD, Levy JK, et al. Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996–2003). J Am Vet Med Assoc 2006;228:559–63.

[22] Nemzek JA, Kruger JM, Walshaw R, et al. Acute onset of hypokalemia and muscular weakness in four hyperthyroid cats. J Am Vet Med Assoc 1994;205:65–8.

[23] Gilroy CV, Horney BS, Burton SA, et al. Evaluation of ionized and total serum magnesium concentrations in hyperthyroid cats. Can J Vet Res 2006;70:137–42.

[24] Hoenig M, Ferguson DC. Impairment of glucose tolerance in hyperthyroid cats. J Endocrinol 1989;121:249–51.

[25] Graham PA, Mooney CT, Murray M. Serum fructosamine concentrations in hyperthyroid cats. Res Vet Sci 1999;67:171–5.

[26] Reusch CE, Tomsa K. Serum fructosamine concentration in cats with overt hyperthyroidism. J Am Vet Med Assoc 1999;215:1297–300.

[27] Connolly DJ, Guitian J, Boswood A, et al. Serum troponin I levels in hyperthyroid cats before and after treatment with radioactive iodine. J Feline Med Surg 2005;7: 289–300.

[28] Randolph JF, DeMarco J, Center SA, et al. Prothrombin, activated partial thromboplastin, and proteins induced by vitamin K absence or antagonists clotting times in 20 hyperthyroid cats before and after methimazole treatment. J Vet Intern Med 2006;14:56–9.

[29] Steiner JM, Petersen MA, Ruaux CG, et al. Serum folate and cobalamin concentrations in cats with hyperthyroidism. [abstract]. J Vet Intern Med 2005;19:474.

[30] Syme HM, Elliott J. Prevalence and significance of proteinuria in cats with hyperthyroidism [abstract]. Presented at the Proceedings of the British Small Animal Veterinary Association. Birmingham (UK), April 3–6, 2003. p. 533.

[31] de Lange MS, Galac S, Trip MRJ, et al. High urinary corticoid/creatinine ratios in cats with hyperthyroidism. J Vet Intern Med 2004;18:152–5.

[32] Mooney CT, Thoday KL, Nicoll JJ, et al. Qualitative and quantitative thyroid imaging in feline hyperthyroidism using technetium-99m as pertechnetate. Vet Radiol Ultrasound 1992;33: 313–20.

[33] Nap AM, Pollak YW, van den Brom WE, et al. Quantitative aspects of thyroid scintigraphy with pertechnetate ($^{99m}TcO_4$-) in cats. J Vet Intern Med 1994;8:302–3.

[34] Peterson ME. Feline hyperthyroidism. Vet Clin North Am Small Anim Pract 1984;14: 809–26.

[35] Sjollema BE, Pollak YW, van den Brom WE, et al. Thyroidal radioiodine uptake in hyperthyroid cats. Vet Q 1989;11:165–70.

[36] Daniel GB, Sharp DS, Nieckarz JA, et al. Quantitative thyroid scintigraphy as a predictor of serum thyroxin concentration in normal and hyperthyroid cats. Vet Radiol Ultrasound 2002;43:374–82.

[37] Henrikson TD, Armbrust LJ, Hoskinson JJ, et al. Thyroid to salivary ratios determined by technetium-99m pertechnetate imaging in thirty-two euthyroid cats. Vet Radiol Ultrasound 2005;46:521–3.

[38] Page RB, Scrivani PV, Dykes NL, et al. Accuracy of increased thyroid activity during pertechnetate scintigraphy by subcutaneous injection for diagnosing hyperthyroidism in cats. Vet Radiol Ultrasound 2005;47:206–11.

[39] Smith TA, Bruyette DS, Hoskinson JJ, et al. Total thyroxine, free thyroxine, pertechnetate scan, and T3 suppression test results in cats with occult hyperthyroidism [abstract]. J Vet Intern Med 1996;10:185.

[40] Marsolais ME, Mott J, Berry CR. Diagnosis of feline hyperthyroidism using thyroid scintigraphy [abstract]. J Vet Intern Med 2003;17:393.

[41] Tomsa K, Hardeggar R, Glaus T, et al. ^{99m}Tc-pertechnetate scintigraphy in hyperthyroid cats with normal serum thyroxine concentrations [abstract]. J Vet Intern Med 2001;15:299.

[42] Nieckarz JA, Daniel GB. The effect of methimazole on thyroid uptake of pertechnetate and radioiodine in normal cats. Vet Radiol Ultrasound 2001;42:448–57.

[43] Fischetti AJ, Drost WT, DiBartola SP, et al. Effects of methimazole on thyroid gland uptake of ^{99m}TC-pertechnetate in 19 hyperthyroid cats. Vet Radiol Ultrasound 2005;46:267–72.

[44] Peterson ME, Becker DV. Radionuclide thyroid imaging in 135 cats with hyperthyroidism. Vet Radiol Ultrasound 1984;25:23–7.

[45] Peterson ME, Melian C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 2001;218:529–36.

[46] Peterson ME, Graves TK, Cavanagh I. Serum thyroid hormone concentrations fluctuate in cats with hyperthyroidism. J Vet Intern Med 1987;1:142–6.

[47] Broome MR, Feldman EC, Turrel JM. Serial determination of thyroxine concentrations in hyperthyroid cats. J Am Vet Med Assoc 1988;192:49–51.

[48] Peterson ME, Gamble DA. Effect of nonthyroidal illness on serum thyroxine concentrations in cats: 494 cases. J Am Vet Med Assoc 1988;197:1203–8.

[49] McLoughlin MA, DiBartola SP, Birchard SJ, et al. Influence of systemic nonthyroidal illness on serum concentration of thyroxine in hyperthyroid cats. J Am Anim Hosp Assoc 1993;29:227–34.

[50] Mooney CT, Little CJ, Macrae AW. Effect of illness not associated with the thyroid gland on serum total and free thyroxine concentrations in cats. J Am Vet Med Assoc 1996;208:2004–8.

[51] Peterson ME, Ferguson DC. Effect of glucorticoids on thyroid function in normal cats and cats with hyperthyroidism [abstract]. J Vet Intern Med 1989;3:123.

[52] Syme HM, Elliott J, Dixon RM. Evaluation of free thyroxine measurement for the diagnosis of hyperthyroidism in cats with chronic renal failure [abstract]. J Vet Intern Med 2002;16:633.

[53] Moore KL, Syme H, Groves E, et al. Use of endogenous thyroid stimulating hormone measurement to diagnose hyperthyroidism in cats with chronic renal failure [abstract]. Presented at the Proceedings of the British Small Animal Veterinary Association. Birmingham (UK), April 1–4, 2004. p. 521.

[54] Otero T, Archer J, Billings H, et al. Serum TSH in hyperthyroid cats pre- and post-therapy [abstract]. Presented at the Proceedings of European Congress of Veterinary Internal Medicine–Companion Animals/European Society of Veterinary Internal Medicine. Munich (Germany), September 19–23, 2002. p. 173.

[55] Rayalam S, Eizenstat LD, Hoenig M, et al. Cloning and sequencing of feline thyrotropin (fTSH): heterodimeric and yoked constructs. Domest Anim Endocrinol 2006;30:203–17.

[56] Rayalam S, Eizenstat LD, Davis RR, et al. Expression and purification of feline thyrotropin (fTSH): Immunological detection and bioactivity of heterodimeric and yoked glycoproteins. Domest Anim Endocrinol 2006;30:185–202.

[57] Mooney CT, Thoday KL, Doxey DL. Serum thyroxine and triiodothyronine responses of hyperthyroid cats to thyrotropin. Am J Vet Res 1996;57:987–91.

[58] Stegeman JR, Graham PA, Hauptman JG. Use of recombinant human thyroid-stimulating hormone for thyrotropin-stimulation testing of euthyroid cats. Am J Vet Res 2003;64:149–52.

[59] Peterson ME, Broussard JD, Gamble DA. Use of the thyrotropin releasing hormone stimulation test to diagnose mild hyperthyroidism in cats. J Vet Intern Med 1994;8:279–86.

[60] Tomsa K, Glaus TM, Kacl GM, et al. Thyrotropin-releasing hormone stimulation test to assess thyroid function in severely sick cats. J Vet Intern Med 2001;15:89–93.

[61] Peterson ME, Graves TK, Gamble DA. Triiodothyronine (T3) suppression test. An aid in the diagnosis of mild hyperthyroidism in cats. J Vet Intern Med 1990;4:233–8.

[62] Refsal KR, Nachreiner RF, Stein BE, et al. Use of the triiodothyronine suppression test for diagnosis of hyperthyroidism in ill cats that have serum concentration of iodothyronines within normal range. J Am Vet Med Assoc 1991;199:1594–601.

[63] Peterson ME, Randolph JF, Mooney CT. Endocrine diseases. In: Sherding RG, editor. 2nd edition, The cat. Diseases and clinical management, vol. 2. New York: Churchill Livingstone; 1984. p. 1403–506.

[64] Wisner ER, Theon AP, Nyland TG, et al. Ultrasonographic examination of the thyroid gland of hyperthyroid cats: comparison to ^{99m}TcO$_4$- scintigraphy. Vet Radiol Ultrasound 1994;35:53–8.

[65] Drost WT, Mattoon JS, Weisbrode SE. Use of helical computed tomography for measurement of thyroid glands in clinically normal cats. Am J Vet Res 2006;67:467–71.