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Evaluation of Thyroid-Stimulating Hormone, Total Thyroxine, and Free Thyroxine Concentrations in Hyperthyroid Cats Receiving Methimazole Treatment

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Background: Iatrogenic hypothyroidism (IH) after treatment of hyperthyroidism can impair renal function. No study compared the efficacy of measurement of serum free thyroxine by equilibrium dialysis (fT4ed) or thyroid-stimulating hormone (TSH) concentrations for monitoring cats receiving methimazole.

Objectives: To (1) compare the ability of total T4 and fT4ed concentrations in conjunction with TSH to define thyroid function in hyperthyroid cats receiving methimazole, (2) determine the prevalence of IH in cats receiving methimazole, and (3) examine the relationship between thyroid axis hormones and serum creatinine concentration.

Animals: One hundred and twenty-five serum samples from hyperthyroid cats receiving methimazole and total T4 concentrations ≤3.9 μg/dL.

Methods: Total T4, fT4ed, and TSH concentrations were measured to evaluate thyroid status and serum creatinine concentration was measured to assess renal function. A low total T4 or fT4ed concentration in combination with an increased TSH concentration defined IH.

Results: Forty-one cats (33%) had increased TSH concentrations. Of cats with total T4 and fT4ed concentrations below the reference range, 68% and 73%, respectively, had TSH concentrations above the reference range. Only 18% of cats with a normal TSH concentration had an increased serum creatinine concentrations as compared to 39% of those with increased TSH concentrations ($P < .001$).

Conclusions: Free T4ed does not identify more cats with potential IH as compared to total T4. The IH prevalence was approximately 20%. Measurement of TSH may be more helpful in indicating that azotemia, if present, is at least in part related to IH. Investigation is needed to define TSH assay utility in identifying possible subclinical IH.

Key words: Creatinine; Hypothyroidism; Subclinical.

The interplay between hyperthyroidism and renal function has been extensively studied in cats. Hyperthyroidism increases glomerular filtration rate (GFR),[1] and its treatment results in a subsequent decrease in GFR.[2–4] When underlying kidney disease is present, the decrease in GFR can contribute to development of azotemia and decreased survival time; iatrogenic hypothyroidism (IH) after treatment for hyperthyroidism may play a role.[5] Approximately 15–17% of cats receiving methimazole[6] and 33–49% of cats treated with radioactive iodine (^{131}I) or bilateral thyroidectomy became azotemic within 6 months of treatment initiation.[2–7] Pre-existing azotemia can decrease overall survival times in cats treated for hyperthyroidism.[8] On the other hand, treatment of IH may improve renal function.[9]

Despite the potential link between IH and azotemia, the best means of monitoring cats after treatment has not been determined. Iatrogenic hypothyroidism potentially could be defined best as the presence of a low serum thyroid hormone concentration in combination with the appropriate physiological response of an increased TSH concentration. Clinical hypothyroidism can be difficult to judge, because after resolution of hyperthyroidism, cats are expected to sleep more, eat less and gain weight, signs also consistent with hypothyroidism. To our knowledge, only a single study has measured total T4 and TSH concentrations in cats receiving medical treatment for hyperthyroidism. Surprisingly, 48% of cats had a combination of low total T4 and increased TSH concentrations,[5] suggesting IH may be common. The prevalence of IH has not been confirmed in an independent study, to our knowledge.

Abbreviations:

fT4ed	free thyroxine measured by equilibrium dialysis
TSH	thyroid stimulating hormone
IH	iatrogenic hypothyroidism
SH	subclinical hypothyroidism
GFR	glomerular filtration rate
NTI	nonthyroidal illness

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Measurement of serum total thyroxine concentration (T4) is commonly used for therapeutic monitoring. Total T4 concentrations can be difficult to evaluate, however. Given that cats with hyperthyroidism are older and more likely to have other diseases, especially renal disease, total T4 concentration may be below the reference range even if IH is not present.[10–13] Serum free thyroxine concentration as measured by equilibrium dialysis (fT4ed) may be a better marker of thyroid function than total T4 concentration.[11] To our knowledge, fT4ed concentrations during treatment with methimazole have not been evaluated to determine if they are easier to interpret than total T4 concentrations. If fT4ed concentrations, as compared to total T4 concentrations, are more likely to be normal in cats with TSH concentration, creatinine concentrations, or both within the reference range, fT4ed may be a better measure of thyroid status in cats receiving methimazole treatment.

Nonthyroidal illness (NTI) and age are not expected to increase TSH concentrations in the majority of patients. In dogs, for example, approximately only 10% of euthyroid patients with nonthyroidal disease have increased TSH concentrations[14]; euthyroid cats with chronic kidney disease do not have increased TSH concentrations.[10] If high TSH concentrations are common in cats receiving methimazole treatment and the combination of a low total T4 or fT4ed concentration together with a high TSH concentration is associated with azotemia, veterinarians should routinely measure TSH concentrations in cats receiving methimazole, which is not the current practice.

The primary objectives of this study were: (1) to determine the prevalence of IH in an independent study with a large number of cats receiving methimazole treatment, (2) to compare the ability of total T4 and fT4ed concentrations in conjunction with TSH concentrations to define thyroid function status in hyperthyroid cats receiving methimazole, and (3) to examine the relationship between thyroid axis hormones and serum creatinine concentration. A secondary objective was to evaluate a possible association between the dose of methimazole and IH and azotemia. We hypothesized that serum fT4ed concentrations would be a better marker of thyroid function than total T4. Accordingly, fT4ed concentration would be below the reference range in more cats with an increased TSH concentration as compared to total T4 concentrations, thus identifying more cats with IH than identified by total T4. We further hypothesized that fT4ed concentrations would more closely correlate (negatively) with serum creatinine concentration as compared to total T4 or TSH.

Materials and Methods

Cats

A total of 125 serum samples from previously diagnosed hyperthyroid cats receiving methimazole treatment and with total T4 concentrations ≤3.9 μg/dL (ie, within or below the reference range) were included. Samples had been submitted consecutively to the diagnostic laboratories at Auburn University (n = 18) and Michigan State University (n = 107) between May 5 and October 25, 2012. Samples with sufficient volume for performance of all assays were used.

Experimental Protocol

All cats were receiving methimazole at the time of sample submission; doses ranged from 1.25 mg PO q24 h to 10 mg PO q12 h. Serum samples were submitted for routine evaluation of treatment and were frozen at −20°C until used for the study. For the study, all samples were reanalyzed at a single laboratory (see below). Age, breed, and sex of the cats and methimazole dose were obtained from the sample submission forms when provided. Reference ranges were 0.8–3.9 μg/dL, 0.8–3.9 ng/dL, and <0.3 ng/mL for total T4, fT4ed, and TSH concentrations, respectively. Lower reference ranges (ie, the lower half of the reference range) for total T4 and fT4ed were 0.8–1.9 μg/dL and 0.8–1.9 ng/dL, respectively. Higher reference ranges (ie, the higher half of the reference range) for total T4 and fT4ed were 2.0–3.9 μg/dL and 2.0–3.9 ng/dL. The reference range for serum creatinine concentration was ≤2.0 mg/dL.

Assay Procedures

Total T4 and fT4ed concentrations were measured by assays,[a,b] previously validated in cats.[11,15,16] Circulating concentrations of TSH in feline serum were measured[c] with a commercially available immunoradiometric assay for canine TSH[d] that displays binding for feline TSH. Sample volumes and assay procedures were carried out according to the manufacturer's protocol. Two pools of feline serum using clinical samples selected as having low or normal concentrations of thyroid hormones were made for validation studies. The "high-TSH" and "normal-TSH" pools had respective mean concentrations of 2.8 and 0.1 ng/mL across repeatability studies. When aliquots of the "high-TSH" pool were diluted with assay zero standard at rates of 1:2, 1:4, and 1:8, the percentages observed/expected results for the dilutions were 106%, 129%, and 133%, respectively. When aliquots of the "high-TSH" pool were mixed with the "normal-TSH" pool at rates of 1:2, 1:4, and 1:8, the percentages of observed/expected results were 114%, 105%, and 92%, respectively. The respective intraassay coefficients of variation for 11 replicates of the "high-TSH" and "normal-TSH" pools were 1.3% and 14%. The respective interassay coefficients of variation for the "high-TSH" and "normal-TSH" pools were 2.9% and 9.7% across 8 assays.

To set the reference range, samples from 50 cats with were used. Twenty-one of the samples were from young adult, clinically healthy, neutered laboratory cats. Eight of the samples were from historically healthy cats; serum had been submitted for feline virus screening and viral tests were negative. The remaining 21 samples were clinical samples from cats with normal baseline thyroid hormone concentrations and normal response to a T3 suppression test (ie, suppression of the total T4 concentration to <1.6 μg/dL after administration of 20 μg liothyronine sodium [T3] 3 times daily for 2 days, then 20 μg liothyronine sodium on day 3, given 2–4 hours before sampling). The TSH concentrations from the clinical samples submitted for thyroid testing were compared with those of the other cats, and were not significantly different. Thus, they were combined to represent a group of cats with normal thyroid function. A reference range of 0–0.32 ng/mL was established using the 2.5–97.5 percentiles of the data set.

A single batch was run for each hormone when possible. The sensitivities of the assays were 0.5 μg/dL and 0.4 ng/dL for total T4 and fT4ed, respectively. For statistical purposes, concentrations below the sensitivity of the assays were set at 0.25 μg/dL for total T4 and 0.2 ng/dL for fT4ed. For TSH, results were not

extrapolated below the concentration of the lowest standard and were reported as 0.1 ng/mL; concentrations above the highest standard (12.3 ng/mL) were reported as 13 ng/mL. Serum creatinine concentration was measured by an automated analyzer.[e]

Statistical Analyses

The Shapiro-Wilk test was used to evaluate normality of data, and the data were determined to be nonparametric. The Mann-Whitney test was used to compare total T4 and fT4ed concentrations as well as methimazole dose between cats with a TSH concentration within or above the reference range. Nonparametric correlation was tested using a Spearman Rank Order test. The correlations were qualified using the following scale: $r = 0$–0.10 was no correlation, $r = 0.11$–0.30 was a weak correlation, $r = 0.31$–0.70 was a moderate correlation, and $r > 0.71$ was a strong correlation. Frequencies were compared among groups using a Chi-squared test. Data are expressed as median (range). Significance for all tests was set at the $P < .05$ level.

Results

Patient Population

Cats included 59 spayed females, 1 intact female, 59 castrated males, and 1 intact male; sex was not specified for 5. The breeds represented included 87 domestic short hair, 19 domestic long hair, 7 domestic medium hair, 4 Siamese, 2 Siamese crosses, 2 Himalayans, 1 Burmese and 3 unknown. Ages ranged from 6 to 20 years (median, 14.5; mean, 14.3) for 123 cats and were not provided for the remaining 2.

Relationship between Total T4, fT4ed, and TSH

The median total T4 concentration for all cats was 1.2 (range, 0.2–3.7) μg/dL. Of 38 cats with total T4 concentrations below the reference range, 26 (68%) had TSH concentrations above the reference range. For cats with TSH concentrations above and within the reference range, the median total T4 concentrations were 0.5 (range, 0.2–3.1) μg/dL and 1.7 (range 0.2–3.7) μg/dL, respectively, which were significantly different ($P < .001$; Fig 1). The median fT4ed concentration for all cats was 1.4 (range, 0.2–6.0) ng/dL. Of 30 cats with low fT4ed concentrations, 22 (73%) had increased TSH concentrations. For cats with TSH concentrations above and within the reference range, the median fT4ed concentrations were 0.6 (range, 0.2–2.7) ng/dL and 1.9 (range, 0.2–6.0) ng/dL, respectively, which were significantly different ($P < .001$; Fig 1). The TSH concentrations were within reference limits for 84 cats (0.1 [range, 0.1–0.3] ng/mL) and above reference range for 41 (1.6 [range, 0.4–13] ng/mL). Fifteen cats (12%) and 19 cats (15%) had an increased TSH concentration and a total T4 and fT4ed concentration, respectively, within the reference range. Thirteen cats (10%) had increased TSH concentrations and both total T4 and fT4ed were within the reference range. If defining IH by a combination of a low total T4 concentration or low fT4ed concentration with increased TSH concentration, the prevalence of IH in this study was 20.8% or 17.6%, respectively.

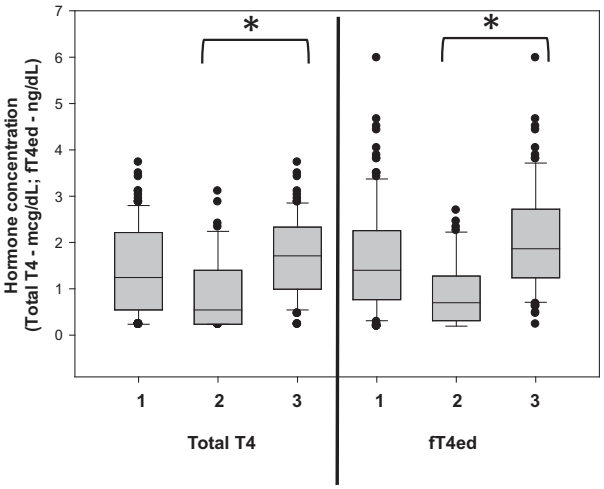

Fig 1. Total T4 and fT4ed concentrations in hyperthyroid cats receiving methimazole. Group 1 = all cats (n = 125); Group 2 = cats with TSH above the reference range (n = 41); Group 3 = cats with TSH within the reference range (n = 84). Groups connected by a bracket with an asterisk are significantly different (Mann-Whitney test; $P < .001$). Each box represents the interquartile (ie, 25th to 75th percentile) range, the horizontal line within the box represents the median value, the bars represent the 10th to 90th percentile, and the circles represent outlying data points.

T4 and fT4ed concentrations were significantly and strongly positively correlated ($P < .0001$, $r = 0.842$; data not shown). Total T4 and fT4ed concentrations each were significantly negatively and moderately correlated with TSH concentration ($P < .0001$ for both; $r = -0.412$ and -0.533, respectively; data not shown).

The percentage of cats with a TSH concentration above the reference range was significantly different ($P < .001$) among cats with a total T4 concentration below the reference range, within the lower half of the reference range and within the upper half of the reference range (ie, <0.8 μg/dL, 0.8–1.9 μg/dL, and >1.9 μg/dL; Table 1). Similarly, the percentage of cats with a TSH concentration above the reference range was significantly different ($P < .001$) among cats with a fT4ed concentration <0.8 ng/dL, 0.8–1.9 ng/dL, and >1.9 ng/dL. When comparing cats with a total T4 concentration below the reference range to cats with a fT4ed concentration below the reference range, no significant difference was detected with regard to the percentage of cats with TSH concentrations within or above the reference range.

Relationship between Thyroid Hormones and Creatinine Concentration

The serum creatinine concentration in cats with a total T4 concentration below the reference range (1.7 [range, 0.6–3.5] mg/dL) was not significantly different ($P = .063$) than the serum creatinine concentration in cats with a total T4 concentration within the reference range (1.6 [range, 0.4–3.6] mg/dL; Fig 2). The serum

Table 1. Percentage of cats with TSH concentrations above or within the reference range as categorized by total T4 and fT4ed concentration. For total T4, below the reference range = <0.8 μg/dL; lower half of the reference range = 0.8–1.9 μg/dL; and upper half of the reference range = 2.0–3.9 μg/dL. For fT4ed, below the reference range = <0.8 ng/dL; lower half of the reference range = 0.8–1.9 ng/dL; and upper half of the reference range = 2.0–3.9 ng/dL. *The distribution of cats with TSH concentration within or above the reference range was significantly different between the concentration ranges for both total T4 and fT4ed.

	TSH Concentration Categorized by Total T4 Concentration		TSH Concentration Categorized by fT4ed Concentration	
Concentration Range T4 or fT4ed	% Within the Reference Range (n = 84)	% Above the Reference Range (n = 41)	% Within the Reference Range (n = 84)	% Above the Reference Range (n = 41)
Below the reference range*	32 (n = 12)	68 (n = 26)	27 (n = 8)	73 (n = 22)
Lower half of the reference range*	78 (n = 38)	22 (n = 11)	70 (n = 38)	30 (n = 16)
Upper half of the reference range*	89 (n = 34)	11 (n = 4)	93 (n = 38)	7 (n = 3)

creatinine concentration in cats with a fT4ed concentration below the reference range (1.7 [range, 0.6–3.5] mg/dL) was significantly different than the serum creatinine concentration in cats with a fT4ed concentration within the reference range (1.5 [range, 0.4–3.6] mg/dL; $P = .033$). The serum creatinine concentration in cats with a TSH concentration above the reference range (2.0 [range, 0.7–3.5] mg/dL) was significantly different than the serum creatinine concentration in cats with a TSH concentration within the reference range (1.6 [range, 0.4–3.6]) mg/dL; $P < .001$).

The distribution of cats with an increased serum creatinine concentration did not change significantly with the total T4 and fT4ed concentration (Table 2). However, the distribution did change significantly with TSH concentration ($P = .019$); 18% (15/84) and 39% (16/41) of cats with a TSH concentration within and above the reference range, respectively, had a serum creatinine concentration above the reference range.

Total T4 and fT4ed concentrations each were significantly but weakly negatively correlated with serum creatinine concentration ($P = .037$ and 0.001, respectively; $r = -0.187$ and -0.290, respectively; data not shown). Serum creatinine and TSH concentrations had a significant positive, but weak correlation with each other ($P = .0009$; $r = 0.294$; data not shown).

Relationship between Methimazole Dose and Thyroid Function

Dose information was available for 113 cats. The dose ranged from 2.5 mg total/cat/day to 20 mg total/cat/day with a median of 5 mg/cat/day. Fifteen different dosing regimens were reported with doses being given 1 (13 cats, 12%), 2 (99 cats, 88%), and 3 (1 cat <1%) times daily. The median doses for cats with a total T4 concentration below the reference range and within the reference range were 7.5 mg/cat/day (range, 5–15) and 5 mg/cat/day (range, 2.5–20), respectively. Cats with a low total T4 concentration received a significantly higher dose of methimazole ($P = .018$) than cats with a total T4 concentration within the reference range, but dose was not significantly different when comparing cats with a TSH concentration in the reference range to those with an increased TSH concentration. A significant correlation between dose and serum creatinine concentration was not detected.

Discussion

In this study, we determined that approximately 20% of cats had IH if defined as a combination of a low thyroid hormone concentration and an increased TSH

Table 2. Percentage of cats with serum creatinine concentrations above or within the reference range as categorized by total T4 and fT4ed concentration. For total T4, below the reference range = <0.8 μg/dL; lower half of the reference range = 0.8–1.9 μg/dL; and upper half of the reference range = 2.0–3.9 μg/dL. For fT4ed, below the reference range = <0.8 ng/dL; lower half of the reference range = 0.8–1.9 ng/dL; and upper half of the reference range = 2.0–3.9 ng/dL. The reference range for serum creatinine concentration was ≤2.0 mg/dL.

	Serum Creatinine Concentration Categorized by Total T4 Concentration		Serum Creatinine Concentration Categorized by fT4ed Concentration	
Concentration Range T4 or fT4	% Within the Reference Range (n = 94)	% Above the Reference Range (n = 31)	% Within the Reference Range (n = 90)	% Above the Reference Range (n = 30)
Below the reference range	66 (n = 25)	34 (n = 13)	67 (n = 20)	33 (n = 10)
Lower half of the reference range	82 (n = 40)	18 (n = 9)	74 (n = 40)	26 (n = 14)
Upper half of the reference range	76 (n = 29)	24 (n = 9)	83 (n = 30)	17 (n = 6)

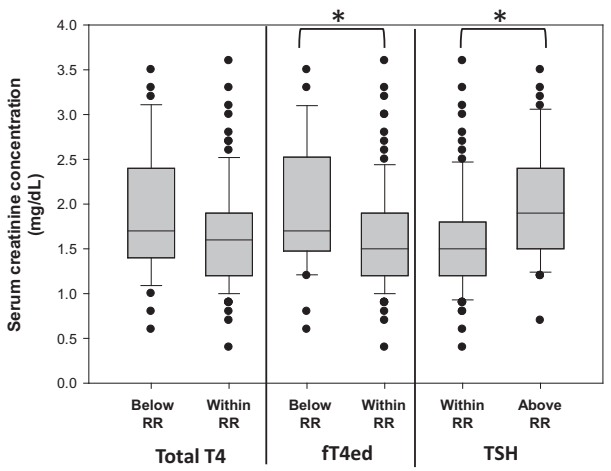

Fig 2. Serum creatinine concentrations in hyperthyroid cats receiving methimazole. RR = reference range. See Figure 1 for explanation of plot.

concentration. Of those cats with a low total T4 or fT4ed concentration, approximately 70% had an increased TSH concentration. Overall, measurement of fT4ed concentration was not a better indicator of the presence of IH than was total T4 concentration in cats being treated with methimazole. Of cats with an increased TSH, the percentage of cats with a low total T4 concentration was not different than the percentage of cats with a low fT4ed concentration. Cats with an increased TSH concentration were more likely to be azotemic than cats with a normal TSH concentration. The percentage of cats with azotemia did not change in relation to total T4 or fT4ed concentrations (ie, whether they were within the reference range or not). The development of a low total T4 concentration but not of azotemia was related to methimazole dose.

In the past, a total T4 concentration below the reference range after treatment for hyperthyroidism often was interpreted as being because of nonthyroidal illness (NTI) and not IH. After radioactive iodine treatment, although 11% of cats had a low total T4 concentration, only 2% had clinical signs of hypothyroidism.[17] Differentiating resolution of hyperthyroidism and onset of hypothyroidism can be challenging because the clinical presentations are similar. However, if a strict definition of IH is applied (ie, by a combination of increased TSH and low total T4 concentrations), a study found that 48% of cats receiving methimazole were affected.[5] In this study, approximately 20% of cats met the criteria for IH. The difference between the studies may be because of the duration of treatment. Cats in the previous study by Williams had been receiving methimazole for 6 months[5] whereas duration of treatment in our study was not limited and some cats may have been on treatment for <6 months. Because hyperthyroidism can lead to atrophy of pituitary thyrotrophs, patients early in the course of methimazole treatment still may have suppressed TSH concentrations.[5] In this study, cats in the first 1–3 months of treatment may have had TSH concentrations within reference range despite low total T4 or fT4ed; with more time TSH concentration may have become increased.

The prevalence of IH reported previously[5] and that reported in this study likely are underestimated. Hypothyroidism potentially exists in some cats with low total T4 and fT4ed concentrations but a TSH concentration within the reference range. The TSH assay, developed for dogs, even fails to recognize hypothyroidism in dogs. Unfortunately, no feline-specific TSH assay has been developed and the canine assay is insensitive, measuring approximately 35% of feline TSH.[18] However, a heterologous assay has been validated in cats and the results correlate clinically with total T4 concentrations.[5,10,18] In this study, TSH concentrations in cats with a total T4 concentration below the reference range were significantly higher than those in cats with a total T4 concentration within the reference range. In addition, a significantly higher percentage of cats with a total T4 concentration below the reference range had a TSH concentration above the reference range (68% [26 of 38 cats]) than did cats with a total T4 concentration within the reference range (17% [15 of 87 cats]). Similarly, previous studies found TSH concentrations to fit expectations, with low TSH concentrations in hyperthyroid cats[10,19] and high TSH concentrations in cats previously treated with radioactive iodine.[5] Thus, measurement of TSH concentrations in cats is clinically useful. Furthermore, our results suggest that, even given the limitations of the TSH assay in cats, a high percentage of cats receiving methimazole that have low total T4 concentrations may be hypothyroid as compared to having low total T4 concentrations for other reasons such as NTI; NTI most commonly is described with decreases in total T4 and fT4 with normal TSH concentrations. Unfortunately, given the retrospective nature of our study, information on other medications being administered that could suppress thyroid hormone concentrations or the presence of NTI was not available.

Given the detrimental effects of hypothyroidism on renal function and survival identified in other studies, consideration should be given to lowering the methimazole dose in cats with low total T4 and increased TSH concentrations, whether or not they have clinical signs of hypothyroidism. In a study, cats with IH were more likely to be azotemic, and the median survival time of hypothyroid azotemic cats (456 days) was significantly shorter than that of hypothyroid nonazotemic cats (975 days).[5] Correction of IH caused a significant decrease in serum creatinine concentration and, in 50% of cats, resolution of azotemia.[9] Thus, monitoring for IH by measurement of both total T4 and TSH concentrations is crucial to minimize azotemia. Whether or not correction of IH also will improve survival remains to be determined.

In a previous study[5] as well as ours, TSH concentrations were increased in a subset of patients that had total T4 and fT4 concentrations within the reference range. The overall percentage of cats with an increased TSH concentrations in this study was 33% (41/125), which is similar to the 35% determined in previous studies of cats treated with both ^{131}I as well as chronic methimazole treatment and thyroidectomy.[5,9,c] In humans, the presence

of thyroid hormone concentrations within the reference range in combination with a TSH concentration above the reference range results in a diagnosis of subclinical hypothyroidism (SH), and SH is linked to renal insufficiency and an increase in all-cause mortality.[20,21] In our study, the percentage of cats with increased TSH concentrations was significantly higher in those with total T4 and fT4ed concentrations in the lower half of or below the reference range compared to those with concentrations in the upper half of the reference range. Thus, a low normal total T4 or fT4ed concentration in combination with an increased TSH concentration also may represent SH in cats, but further study is required for confirmation. In the meantime, given the association of SH and mortality in humans,[20,21] if a cat has a total T4 concentration in the lower half of the reference range and an increased TSH concentration, consideration should be given to lowering the methimazole dose.

Other possible causes for increased TSH concentrations in cats with total T4 concentrations within the reference range are artifactual errors or the presence of NTI. Hospitalized humans can have TSH concentrations above the reference range as a result of NTI, and the TSH concentration returns to the reference range after recovery and discharge from the hospital.[22] A small percentage of dogs with NTI can have TSH concentrations above the reference range.[14] Because TSH concentrations did not normalize in some cats suspected of IH after supplementation with thyroxine and a total T4 concentration in the upper half of the reference range,[23] SH is not present in all cats with increased TSH concentrations. In a study, cats with chronic kidney disease did not have increased TSH concentrations.[10] The prevalence of increased TSH concentrations in cats with NTI of any cause has not been studied to our knowledge.

Although total T4, fT4ed, and TSH concentrations correlated significantly with serum creatinine concentrations, the correlation was weak. Serum creatinine concentrations were significantly different between cats with a fT4ed concentration within or below the reference range and cats with a TSH concentration within or above the reference range. Although populations overlapped, the amount of overlap was less when cats were classified by TSH concentration. In addition, although the percentage of cats with a serum creatinine concentration above the reference range was not significantly different between cats grouped by total T4 or fT4ed concentrations, the percentage of cats with serum creatinine concentrations above the reference range was significantly lower in cats with normal TSH concentrations (18%) as compared to those with increased concentrations (39%). Thus, TSH concentration may be a better indicator in cats receiving methimazole that treatment is causing IH and potentially contributing to azotemia. Alternatively, TSH has been shown to be increased in 20% of people with chronic renal failure[20] and may be the result instead of the cause of the changes in serum creatinine concentration (ie, secondary to NTI). Further study is needed to determine if decreasing the dose of methimazole lowers the TSH concentration and decreases azotemia.

The median methimazole dose for cats with a total T4 concentration within the reference range was 5 mg/cat/day (range, 2.5–20). Cats with low serum total T4 concentrations received significantly higher doses of methimazole ($P = .015$) than cats with total T4 concentrations within the reference range but dose was not significantly different when comparing cats with TSH concentrations in the reference range to those with increased TSH concentrations. In an early publication on treatment of hyperthyroid cats with methimazole, the median dose required was 10 mg/cat/day (range, 2.5–20).[24] Thus, the doses required may have decreased over time, perhaps because of earlier diagnosis and treatment (ie, lower doses required with milder disease). Accordingly, veterinarians should be conservative with the initial prescribed dose of methimazole.

This study had several limitations. As discussed above, the TSH assay is not species-specific, likely underestimating the incidence of IH. The retrospective nature of the study as well as the lack of data on clinical signs of hypothyroidism, other medications administered and presence of NTI make interpretation of the findings more difficult. In addition, information regarding duration of methimazole treatment was lacking. The possibility for persistent pituitary thyrotroph atrophy also may have led to an underestimation of the percentage of cats with IH.

In conclusion, our findings suggest that IH may be common in cats receiving methimazole treatment for treatment of hyperthyroidism, especially in those with total T4 or fT4ed concentrations below the reference range. Measurement of fT4ed concentration does not identify more cats with increased TSH and possible IH as compared to total T4 concentration. Measurement of TSH may be more helpful in indicating that azotemia, if present, is at least in part related to IH. Given the limitations of TSH measurement, a total T4 concentration, fT4ed concentration or both always must be measured together with the TSH concentration, and all hormone concentrations interpreted together. Because some cats had TSH concentrations above the reference range despite having total T4 or fT4ed concentrations within the reference range, further investigation is warranted in defining the clinical utility of the TSH assay in identifying SH and its possible role in morbidity and mortality associated with treatment of hyperthyroidism. In the meantime, in cats receiving methimazole treatment that have increased TSH concentrations and total T4 or fT4ed concentrations in the lower half of the reference range or below, consideration should be given to lowering the methimazole dose. Last, methimazole doses used currently are lower than those reported in earlier literature, and consideration should be given to starting methimazole at a low dose.

Footnotes

[a] Coat-A-Count T4 assay, Siemens Medical Solution Diagnostics, Los Angeles, CA.

[b] fT4-ED, Antech Diagnostics, Irvine, CA.
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