# Paired Pre- and Post-treatment Serum Biochemical Parameters and Thyroxine Concentrations in a Cohort of Ninety Seven Radioiodine-treated Hyperthyroid Cats

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## ABSTRACT

Serum hepatic and renal parameters from a 97 hyperthyroid cat cohort, sampled within 2 weeks before and 8-11 weeks after oral radioiodine treatment, were retrospectively reviewed for: 1.relationships between pre-treatment total serum thyroxine concentration (T4) and the biochemical values; 2. degree of value change; and 3. influence of pre-treatment methimazole exposure or concurrent cardiac management drugs on the values. Spearmen's ranked correlation, chi-square, Kruskal-Wallis, and Mann-Whitney techniques were used. Weak statistically significant correlations between the pre-treatment T4 and the degree of ALP, ALT, and AST abnormality and between the degree of post-treatment T4, ALP, and ALT reduction were found. The degree of T4 change was greater in methimazole-exposed and cardiac drug-treated cats. The BUN and creatinine significantly increased post-treatment; about half of the cats became azotemic (varying degrees). No significant relationship was found between the pre-treatment T4 or the T4 reduction and the increase in BUN and creatinine values.

## INTRODUCTION

The clinical phenomenon of feline hyperthyroidism has been studied from many perspectives since it was first documented in the early 1980s.[1] Numerous aspects of the disease have been investigated including diagnostic tests,[2-4] risk parameters,[5] cardiovascular sequellae,[6-8] renal sequellae,[9-11] survival,[12-14] efficacy and radiation safety of systemic Iodine-131 (radioiodine) treatment,[15-17] thyroidectomy,18 medical management,[19-24] and laboratory findings.[25-30] Despite the numerous reports on feline hyperthyroidism, there is limited information on the effect of methimazole on radioiodine treatment results in spontaneously diseased cats.[13,14,22,24]

Similarly, there is limited statistical information on whether pre-treatment or post-treatment routine laboratory parameters are related to the severity of the hyperthyroid condition,[11,31,32] and to what degree they progress or regress following radioiodine treatment in the same population of cats.[28-30,32-34] No study was found in which there were more than 50 cats with paired follow-up laboratory values. Furthermore, in most of the studies, regardless of the number of cats, there were confounding variables including pre-treatment with thyroid suppression drugs.[32,33,35]

Because the decision to treat a hyperthyroid cat with radioiodine is based in part on the evaluation of pre-treatment laboratory values, particularly the severity of the total serum thyroxine concentration (T4) abnormality, the status of routine serum renal parameters and liver enzymes, as well as a clinical assessment of the potential for post-treatment biochemical abnormalities, it seemed germane to evaluate this in a cohort of spontaneously hyperthyroid cats analyzed before and after treatment.

The purpose of this study was two-fold and was focused on a large cohort of minimally managed hyperthyroid cats treated with radioiodine at a private treatment facility that could be retrospectively evaluated. First, a comparison of pre-treatment T4 to routine laboratory parameters before and approximately 2 months after radioiodine treatment was conducted to determine if the magnitude of observed abnormalities was related to a single pre-treatment T4 for: 1. the degree of post-treatment renal-related serum biochemical abnormalities, or 2. the degree of pre-treatment liver-related serum biochemical abnormalities. Secondly, a comparison was made to determine if pre-treatment exposure to methimazole or concurrent treatment with a varied spectrum of cardiac management drugs (deemed necessary due to disease severity) significantly influenced the pre-treatment to post-treatment change in T4 (one before and one after treatment), the T4 post-treatment status 2 months following radioiodine treatment, or the trends in serum biochemical results.

## MATERIALSAND METHODS

Cats (n = 97) included in this retrospective study were presented for hyperthyroid treatment with I131 (radioiodine) at a privately owned, inpatient facility in the years from 2000 through 2003. To be included in the study, the pre-treatment parameters of T4 (as total T4) (ug/dl), body weight (kg), age (years), gender (f, f/s, m m/n), breed, and the serum concentrations of: aspartate aminotransferase (AST) (U/l), alanine transaminase (ALT) (U/l), alkaline phosphatase (ALP) (U/l), total bilirubin (mg/dl), cholesterol (mg/dl), total protein (g/dl), albumin (g/dl), creatinine (mg/dl), urea nitrogen BUN (mg/dl), phosphorus (mg/dl), calcium (mg/dl) acquired within 2 weeks prior to the radioiodine treatment had to be available for analysis.

None of the cats were receiving concurrent thyroid suppression medication (methimazole) at the time of radioiodine treatment and those previously exposed to it had a minimum withdrawal of two weeks from that medication before final pre-treatment T4 testing or radioiodine administration.

The T4 status of the methimazole-exposed cats at the time before the drug was discontinued was not available as pretreatment data and was not included in the analyses. The presence or absence of previous thyroid suppression treatment was classified as methimazole exposure and was included in the pre-treatment database without regard to dose or duration, because those variables were beyond the control of the treatment facility. Again, to be included in the study, the post-treatment parameters for all of the above variables as well as the presence or absence of concurrent cardiac pharmacologic management (beta-adrenergic blocker, calcium channel blocker, or angiotensin-converting enzyme inhibitor individually or in any combination) as prescribed by the facility director [RCW] had to be available for analysis. Because the use of individual vs combinations of drugs was

variable, we chose to consolidate the group into those being managed for cardiac disease regardless of the individualized management protocol, acknowledging that the physiologic effects of the drugs are different. To the authors' knowledge, other drugs that might have influenced the results were not administered, but that possibility has not been unequivocally excluded. Because the cats were isolated for an average of 16.95 +/- 4.61 days, the post-treatment laboratory evaluation occurred between 8 and 11 weeks after oral radioiodine administration. Following radioiodine-related isolation, the cats were managed by referring veterinarians so specific data on the presence or absence of drugs for other conditions was not available.

Only laboratory values including total T4 values from two national/regional commercial veterinary clinical laboratories were accepted. The laboratory used for the pretreatment and post-treatment biochemical assessment had to be the same for a given cat. Statistical analyses were performed on cat data independently for each of the two involved laboratories prior to indexing the variables as defined below to assure trends were the same. To provide insight on the relative laboratory parameter status (including T4) across the two involved laboratories, the numeric values for parameters were indexed as a function of the specified normal range in each laboratory.

The indexing process consisted of setting all individual animal values for each test to 1.0 if the value fell within the specified normal range for that laboratory. If a value exceeded the upper limit of that laboratory's specified normal range, the individual animal value was divided by the maximum normal value and expressed as a value > 1.0. Similarly, if a value was less than the lower limit of that laboratory's specified normal range, the individual animal value was divided by the minimum normal value and expressed as a value < 1.0. Thus, the resulting indexed parameters for all cats were intended to minimize individual laboratory influence. Unless specified otherwise, all laboratory values used in the analysis were indexed. However, the indexed data were treated as continuous variables and were not rounded until all analyses were completed.

Each cat was treated with dosages between 1.13 – 2.07 x 108 Becquerels (3.06 – 6.04 millicuries) of I131 orally in a gelatin capsule. The activity in the gelatin capsule was calibrated from a commercial source to be given to the cat at a specific time. The norm for radioiodine dose was 5.0 mCi/cat in the early phases of the study, and 4.0 mCi/cat in the later phases of the study. Dose adjustments were subjectively based on the variables of body weight and T4 concentration. Therefore, a very small cat (eg, 2 kg) with a T4 less than twice the upper normal limit for the involved laboratory would have received 3.0 mCi. Similarly, a large cat (eg, 6 kg) with a T4 of over three times the upper normal limit for the involved laboratory would have received 6.0 mCi. The average dose in mCi/kg was calculated for the various body typesAll pre-treatment indexed parameters (total T4, AST, ALT, ALP, total bilirubin, cholesterol, total protein, albumin, BUN, creatinine, phosphorus, and calcium concentrations) were statistically compared to the same parameters obtained post-treatment in cats receiving and not receiving concurrent cardiac-related medication, in cats with pre-treatment methimazole exposure, or in cats that had received a combination of these medications. An assessment was made of all indexed and non-indexed pre-treatment variables, all indexed and non-indexed post-treatment variables, and the differences between them (pretreatment minus post-treatment paired for each animal) to determine if their respective distributions were normal using the Kolmogorov-Smirnov test with the Lillefors significance correction.[s] By this analysis, none of the pretreatment variables, none of the post-treatment variables (except total protein and phosphorus), or the differences between then were normally distributed. To further clarify the distribution of the laboratory variables, the differences (post-treatment minus pre-treatment) were subjected to a visual

assessment of Normal Q-Q, and Detrended Normal Q-Q plots.[a]

Based on interpretation of these tests, the differences were not normally distributed for any of the parameters. Therefore, all analyses were performed with the assumption that the data being not normally distributed required the use of non-parametric statistical methods. To determine whether all indexed pre-treatment variables could be pooled, and whether all indexed post-treatment variables could be pooled without regard to previous or concurrent medication status, the respective pre-treatment and post-treatment values were statistically compared using the Kruskal-Wallis test (nonparametric, one-way ANOVA[a] equivalent test) for the four groups defined here (cardiac meds, methimazole exposure, both, no medications). Because differences among some pre-treatment variables were found across the four groups, an acknowledgment was placed in the results tables to delineate those variables within the otherwise pooled groups.

Spearman's Ranked Correlationa technique was used to identify linear relationships among the pre-treatment variables from cats receiving concurrent cardiac-related medication, from cats that had pre-treatment methimazole exposure, from cats treated with both medications, and from cats that had received neither type of medication. A similar analysis was performed on the post-treatment variables and the difference between the pre and post-treatment variables. To further determine if there were statistically significant differences between the pre-treatment and the post-treatment paired indexed variables, a Wilcoxon Signed Ranks testa was utilized.

Finally, to examine the differences between the pre-treatment and post-treatment indexed laboratory variables, the Mann-Whitney test was used to determine if there were statistically significant differences in the degree of laboratory variable change between the unmedicated group and each of the three medicated groups. Gender cross tabulations data were evaluated by Chi-square test of independence. Statistical significance for all analyses was defined as the probability of the null hypothesis (eg, no relationship or no difference) being true was less than 5.0 % ($p < 0.05$).

## RESULTS

The mean age of the 97 cats studied herein was 12.86 years (+/- 2.39 years SD). In general, females (57%) outnumber males except for the group treated with both pre-treatment methimazole exposure and concurrent cardiac drugs. There were some differing trends among the male to female ratio within

***Table 1**. Gender distribution across of ninety seven hyperthyroid cats classified by medication history.*

| Medical History: | Gender | | |
|---|---|---|---|
| | Male (intact or neutered | Female (intact or neutered | TOTAL ( both genders) |
| no medications | 21 | 29 | 50 |
| pre-treatment of methimazole exposure | 9 | 9 | 18 |
| pre-treatment or post-treatment cardiac-related medications* | 6 | 14 | 20 |
| both methimazole and caridac-related medications | 6 | 3 | 9 |
| TOTAL | 42 | 55 | 97 |

** beta-adrenergic blcoker, calcium channel blocker, or angiotensin-converting enzyme inhibitor*

*[a] SPSS Inc, 11.5.1 (2002), Chicago, IL*

the four groups, but the differences were not statistically significant (Table 1). The body weight of the cats ranged from 2.18 to 7.18 kg. The average dose administered was 1.65 mCi/kg for cats weighing between 2 and 4 kg, 1.09 mCi/kg for cats weighing 4 to 6 kg, 0.75 mCi/kg for cats weighing more than 6 kg. These differences acknowledge that the degree of T4 increase above the normal range was subjectively factored in to the dose administered. The range of radioiodine dose for the cats in this study was 0.67 to 2.46 mCi/kg.

Eighteen (18.6%) had prior methimazole exposure, 20 (20.6%) were treated with cardiovascular-related medications during or after radioiodine administration, 9 (9.3%) had both methimazole and cardiac-related medication, and 50 (51.5%) had none of these medications. The indexed mean pre-treatment T4 was 2.53 +/-1.66 times the upper normal limit for each lab (range 1.0 – 14.9; Table 2). The indexed mean post-treatment T4 was 0.93 +/-0.31 times the upper normal limit for each lab (range 0.3 – 3.1; Table 3). Post-treatment, 63 (64.9%) of the T4 values were in normal range, 31 (32.0%) were below normal range, and three (3.1%) were above normal range. However, the indexed pre-treatment T4 was 14.9 for one of the cats above the normal range post-treatment.

***Table 2**. Pre-treatment serum parameters for ninety seven hyperthyroid cats regardless of medication history**

| | Laboratory Values | | | | | | Number of cats with indexed laboratory values more than 2 SD from the group mean | |
|---|---|---|---|---|---|---|---|---|
| | Number of observations | lower than normal range | within normal range | greater than normal range | Indexed** mean value | SD of indexed** mean | >2 SD below | >2 SD above |
| Variable: | | n(%) | n(%) | n(%) | | | n(%) | n(%) |
| Total T4 | 97 | 0 | 1 (1.1) | 96 (99.0) | 2.527 | 1.664 | 0 | 0 |
| AST | 78 | 2 (2.2) | 48 (61.5) | 28 (35.9) | 1.278 | 0.560 | 0 | 4 (5.1) |
| ALT | 94 | 0 | 19 (20.2) | 75 (79.8) | 2.510 | 2.107 | 0 | 5 (5.3) |
| ALP | 94 | 0 | 64 (68.1) | 30 (31.9) | 1.216 | 0.515 | 0 | 3 (3.2) |
| total bilrubin | 81 | 0 | 64 (79.0) | 17 (21.0) | 1.219 | 0.560 | 0 | 3 (3.7) |
| cholesterol | 87 | 0 | 81 (93.1) | 6 (6.9) | 1.015 | 0.067 | 0 | 0 |
| total protein | 91 | 1 (1.1) | 83 (91.2) | 7 (7.7) | 1.003 | 0.019 | 1 (1.1) | 1 (1.1) |
| albumin | 90 | 2 (2.2) | 86 (95.6) | 2 (2.2) | 0.993 | 0.080 | 1 (1.1) | 0 |
| BUN | 93 | 13 (14.0) | 62 (66.7) | 18 (19.4) | 1.044 | 0.191 | 0 | 5 (5.4) |
| creatinine | 93 | 9 (9.7) | 78 (83.9) | 6 (6.5) | 1.001 | 0.142 | 2 (2.2) | 1 (1.1) |
| phosphorus | 88 | 0 | 86 (97.7) | 2 (2.3) | 1.003 | 0.018 | 0 | 0 |
| calcium | 90 | 0 | 86 (95.6) | 4 (4.4) | 1.001 | 0.008 | 0 | 1 (1.1) |

** previous exposure to methimazole, concurrent of subsequent treatment with cardiac-related drugs, both, or no medication [cardiac-related drugs include beta-adrenergic blocker, calcium channel blocker, or angiotensin-converting enzyme inhibitor]*
*[the pre-treatment indexed means for T4 and ALP we not statistically the same among the four medication groups]*
***indexed laboratory values within the normal range are equated to 1.0*
*indexed laboratory values above the normal range are expressed as a multiple of the highest normal value*
*indexed laboratory values below the normal range are expressed as a multiple of the lowest normal value*

***Table 3.*** *Post-treatment serum parameters for ninety seven hyperthyroid cats regardless of medication history**

| | Laboratory Values | | | | | | Number of cats with indexed laboratory values more than 2 SD from the group mean | |
|---|---|---|---|---|---|---|---|---|
| | Number of observations | lower than normal range | within normal range | greater than normal range | Indexed** mean value | SD of indexed** mean | >2 SD below | >2 SD above |
| Variable: | | n(%) | n(%) | n(%) | | | n(%) | n(%) |
| Total T4 | 97 | 31 (32.0 0 | 63 (64.9) | 3 (3.1) | 0.933 | 0.306 | 0 | 0 |
| AST | 80 | 0 | 72 (90.0) | 8 (10.0) | 1.165 | 0.823 | 0 | 4 (5.1) |
| ALT | 88 | 0 | 68 (96.5) | 20 (22.7) | 1.252 | 0.955 | 0 | 5 (5.3) |
| ALP | 86 | 0 | 83 (96.5) | 3 (3.5) | 1.020 | 0.123 | 0 | 3 (3.2) |
| total bilrubin | 83 | 0 | 71 (85.5) | 12 (14.5) | 1.217 | 1.174 | 0 | 3 (3.7) |
| cholesterol | 82 | 0 | 57 (69.5) | 25 (30.5) | 1.062 | 0.139 | 0 | 0 |
| total protein | 85 | 0 | 61 (71.8) | 24 (29.2) | 1.018 | 0.036 | 0 | 1 (1.1) |
| albumin | 84 | 1 (1.2) | 74 (88.1) | 9 (10.7) | 1.005 | 0.021 | 1 (1.2) | 0 |
| BUN | 90 | 3 (3.3) | 34 (37.8) | 53 (58.9) | 1.222 | 0.320 | 0 | 5 (5.4) |
| creatinine | 92 | 0 | 47 (51.1) | 45 (48.9) | 1.268 | 0.712 | 0 | 1 (1.1) |
| phosphorus | 85 | 1 (1.2) | 84 (98.8) | 0 (0.0) | 1.000 | 0.004 | 0 | 0 |
| calcium | 84 | 2 (2.4) | 75 (89.3) | 7 (8.3) | 0.998 | 0.062 | 9 (1.2) | 1 (1.1) |

**previous exposure to methimazole, concurrent of subsquent treatment with cardiac-related drugs, both, or no medication [cardiac-related drugs include beta-adrenergic blocker, calcium channel blocker, or angiotensin-converting enzyme inhibitor]*
***indexed laboratory values within the normal range are equated to 1.0*
*indexed laboratory values within the normal range are expressed as a multiple of the highest normal value*
*indexed laboratory value below the normal range are expressed as a multiple of the lowest normal value*

There was a statistically significant ($p < 0.05$), but very weakly positive correlation (R values ranging from 0.32 to 0.42) between the degree of T4 abnormality and the degree of ALP, ALT, and AST abnormalities pre-treatment. However, this only explained only about 10-15% of the variation (R-square values ranging from 0.10 to 0.18) encountered in these variables. In addition, there was a statistically significant relationship between the reduction in T4 and the reduction in ALP and ALT post-treatment. There was no statistically detectable relationship between T4 abnormality and either BUN or creatinine abnormalities pre-treatment, and there was no statistically detectable relationship between the degree of reduction in T4 and the degree of increase in either BUN or creatinine post-treatment.

There was a statistically significant difference ($p < 0.05$) between the pre-treatment indexed median T4 of the group with methimazole exposure (mean = 3.32, median = 2.34) and those cats in our series without it (mean = 2.07, median =1.85). There was no statistically significant difference between the post-treatment indexed median T4 of those with methimazole exposure (mean = 1.01, median = 1.00) and those cats in our series without it (mean = 0.87, median =

1.00). The pre- to post-treatment change in indexed median T4 was significantly greater ($p < 0.05$) in the cats with methimazole exposure (mean = 2.31, median = 1.49) than in those without it (mean = 1.20, median 0.98). There was no statistically significant difference in the pre-treatment indexed laboratory parameters (excluding T4 and ALP) between the methimazole exposed and unexposed groups (methimazole exposed group had greater T4 and ALP values). There was no statistically significant difference in the any of the post-treatment indexed laboratory parameters between the methimazole exposed and unexposed groups. The pre- to post-treatment change in indexed AST, ALT, total bilirubin, cholesterol, total protein, albumin, BUN, creatinine, phosphorus, and calcium concentrations were not statistically significantly different between those who were methimazole-exposed compared to those who were not (Table 4). However, the pre to post-treatment change in indexed median ALP was statistically significantly different between the methimazole-exposed (mean = 0.22, median = 0.00) and unexposed (mean = 0.11, median =0.00) groups.

There was a statistically significant difference ($p < 0.005$) between the indexed median T4 of the group treated with the cardiac medications (mean = 2.81, median 2.53) and those not treated with the cardiac medications (mean = 2.07, median = 1.85) at pre-treatment assessment. There was, however, no statistically significant difference between the median indexed T4 at post-treatment assessment of those who had been treated with the cardiac medications (mean = 0.95, median =1.00) and those who had not (mean = 0.87, median =1.00). The pre- to post-treatment change in indexed median T4 was statistically significantly greater ($p < 0.01$) in those who were treated with the cardiac medications (mean = 1.86, median = 1.62) than in those who were not treated with the cardiac medications treated (mean = 1.20, median = 0.98). There was no statistically significant difference in the indexed median laboratory parameters (excluding T4 and ALP) between the cardiac medication treated and untreated groups at pre-treatment (excluding T4 and ALP, both of which were greater in the cardiac medications group) or post-treatment assessment (no exceptions).

Similarly, the change (pre- to post-treatment) in AST, ALT, total bilirubin, cholesterol, total protein, albumin, BUN, creatinine, phosphorus, and calcium concentrations was not statistically significantt different between those who were treated with the cardiac medications compared to those who were not. However, the pre- to post-treatment change in indexed median ALP was statistically significantly different between those who were cardiac medication treated (mean = 0.37, median = 0.14) compared to those who were not so treated (mean = 0.11, median = 0.00).

When post-treatment to pre-treatment laboratory parameters were compared across the groups by medical management status (methimazole exposure only, cardiac medications only, both, and neither), there was a statistically significant ($p < 0.02$) decrease in median T4, ALP, ALT, AST, TBili, cholesterol, and total protein, but a statistically significant ($p < 0.05$) increase in median BUN and creatinine (Table 4). Only the liver enzymes (ALT, ALP, AST) were abnormal (high) more than 30% of the time (with ALT being abnormal almost 80% of the time) pre-treatment. However, less than 6.5% were more than two standard deviations above the indexed group mean (Table 2).

Similarly, the total bilirubin and BUN were abnormal (high) about 20% of the time pre-treatment. However, less than 5.5% were more than two standard deviations above the group mean post-treatment. Of the laboratory values analyzed, ALT, cholesterol, and total protein were abnormal (high) 20 to 30% of the time, and the creatinine and BUN were abnormal (high) about 50% of the time post-treatment (Table 4). With few exceptions, comparing post-treatment to pre-treatment values, the T4 and ALT statistically significantly decreased, but the BUN and creatinine statistically significantly increased (Table 4) following radioiodine treatment

***Table 4.*** *Direction of the change (post-value minus pre-value) in serum parameters for ninety seven hyperthyroid cats classified according to medication history**

| | pre-treatment methimazole exposure | | | post-treatment cardiac-related drugs | | | both medications | | | no medications | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | number of observations | change in mean** | p*** value | number of observations | change in mean** | p*** value | number of observations | change in mean** | p*** value | number of observations | change in mean** | p*** value |
| Variable: | | | | | | | | | | | | |
| Total T4 | 18 | ↓ | 0.000 | 20 | ↓ | 0.000 | 9 | ↓ | 0.008 | 50 | ↓ | 0.000 |
| AST | 13 | ↓ | 0.022 | 12 | ↑ | 0.777 | 6 | ↓ | 0.101 | 37 | ↓ | 0.416 |
| ALT | 18 | ↓ | 0.001 | 16 | ↓ | 0.009 | 7 | ↓ | 0.063 | 50 | ↓ | 0.000 |
| ALP | 17 | ↓ | 0.037 | 16 | ↓ | 0.063 | 7 | ↓ | 0.104 | 44 | ↓ | 0.073 |
| total bilrubin | 16 | ↓ | 0.655 | 10 | ↑ | 0.194 | 6 | ↓ | 0.157 | 43 | ↓ | 0.054 |
| cholesterol | 17 | ↑ | 0.148 | 12 | ↑ | 0.128 | 7 | ↑ | 0.418 | 39 | ↑ | 0.005 |
| total protein | 3 | not available | N/A | 5 | not available | not available | 1 | not available | N/A | 17 | ↑ | 0.332 |
| albumin | 16 | ↓ | 0.333 | 13 | ↑ | 0.337 | 8 | no change | N/A | 41 | ↑ | 0.186 |
| BUN | 18 | ↑ | 0.030 | 14 | ↑ | 0.053 | 8 | ↑ | 0.382 | 46 | ↑ | 0.000 |
| creatinine | 18 | ↑ | 0.038 | 15 | ↑ | 0.041 | 8 | ↑ | 0.043 | 48 | ↑ | 0.000 |
| phosphorus | 3 | not available | N/A | 5 | ↓ | 0.374 | 2 | not available | N/A | 15 | ↓ | 0.334 |
| calcium | 17 | ↓ | 0.357 | 12 | no hange | 1.000 | 8 | ↑ | 0.317 | 47 | ↑ | 0.917 |

**previous exposure to methimazole, concurrent or subsequent treatment with cardiac-related drugs, both, or no medication*
*[cardiac-related drugs include beta-adrenergic blocker, calcium channel blocker, or angiotensin-converting enzyme inhibitor]*
***direction trends were the same for mean or median values*
**** p value for Wilcoxon Signed Ranks test used test for differences between median values*

for all management groups. However, less than 4.5% of the cats had abnormal renal-related serum values more than two standard deviations above the indexed mean post-treatment.

## DISCUSSION

There was a statistically significant improvement in routine serum liver parameters and a significant deterioration of the routine serum renal parameters in this cohort of 97 hyperthyroid cats after radioiodine treatment regardless of whether or not they had been treated with either thyroid suppression drugs or cardiac management drugs. The statistically significant difference in the mean reduction of T4 between the methimazole exposed and unexposed groups and between the cardiac medications-treated and non-treated groups is presumed to be a function of clinical disease severity and possibly disease duration. Although, this may be in part a rebound phenomenon due to enhanced radioiodine uptake after methimazole withdrawal, the similar trends seen in the cardiac medications group may bring this into question unless there is a similar and yet to be recognized effect due to the cardiac medications. More controlled prospective investigation of spontaneous disease is indicated because this retrospective study only raises the question. The presence or absence of a methimazole-related enhanced T4 reduction has been previously discussed in normal and spontaneously affected cats.[13,21,23] The data and conclusions from our study, acknowledging its retrospective limitations, do not provide support for a specific "rebound" effect exclusively for the methimazole-exposed group. There was no other statistically significant relationship between either cardiac medicated or methimazole-exposed groups and the remaining laboratory values.

Over all treatment groups, the weak but statistically significant relationship between pre-treatment T4 and the pre-treatment liver-related laboratory values (and the degree of post-treatment change) suggests a probable cause (hyperthyroidism) and effect (liver disease), as well as a severity of disease effect that generally resolves with appropriate treatment. Our observations are similar to a report of only 15 cats, some of which had been exposed to methimazole,[33] and to a report of 45 cats, all of which were treated with carbimazole.[35] Our finding that most of the liver-related enzyme abnormalities resolved post-treatment in all of our categories of treated cats may influence clinical judgment on how extensive additional pre-treatment liver assessments should be and may minimize the likelihood that the liver-related biochemical abnormalities are drug-related.

Similar to our data, previous reports indicate that 50% or more hyperthyroid cats have pre-treatment abnormalities in ALT ( 54 to 91%), AST (56 - 66 %), and ALP (43 to 75%).26,27 Unique to our analysis is that the degree of liver-related biochemical abnormalities had a statistically significant limited, and at least clinically interesting, positive correlation with the degree of T4 abnormality and the same statistically significant relationship was found for the degree of change (decrease) in these liver-related values following treatment. A report of 34 hyperthyroid cats identified a statistically significant relationship only between pre-treatment ALP and pre-treatment T4.[36] These and our observations further suggest that great care should be observed in determining the relevance of abnormal liver-related biochemical values when making a radioiodine treatment decision.

It has been stated that objective data on how common azotemia is following radioiodine treatment for feline hyperthyroidism is lacking,[11] but reports of renal function compromise in cats following radioiodine treatment are common.[4,11,26,27,30,32] A mild increase in BUN is common in untreated hyperthyroid cats, but is poorly correlated with the development of azotemia post-treatment.[11] Previous reports vary on the occurrence of pre-treatment azotemia with BUN abnormalities ranging from 27 to 71%, and creatinine abnormalities up to 20%. As for the liver-related biochemical parameters,

our values were similar, but the degree of abnormalities among the individual parameters varied.[26,27]

One review suggests that overt renal failure occurs in approximately 30% of cats treated for hyperthyroidism within 30 days after treatment, but that the creatinine remains stable thereafter at +/- 2.1 mg/dl when reassessed at 1year.30 This lack of progressive renal dysfunction is corroborated by another 21-cat study in which only five had post-treatment renal dysfunction.[32] Our data suggest a similar frequency of renal-related biochemical abnormalities. The question, however, is whether the degree of renal dysfunction is sufficient to either preclude radioiodine treatment or to require aggressive post-treatment medical intervention? Unfortunately, our study failed to uncover any useful trend between single sample pre-treatment T4 and any of the pre-treatment, post-treatment or change (pre-treatment minus post-treatment) BUN or creatinine values or the risk of clinically relevant post-treatment renal failure.

We acknowledge that our analyses were based on only one pre-treatment and one post-treatment T4 sample, and that there is some fluctuation in this parameter, even during times of the day. However, an earlier report of 39 hyperthyroid cats subjected to various treatments indicated that there was no difference between the pre-treatment T4, BUN, or creatinine between cats that progressed to renal failure post-treatment and those that did not.[31] One study of 21 cats, nine of which had pre-treatment exposure to anti-thyroid drugs, did find a statistically significant, formulaicallyderived relationship between a single pre-treatment T4 and either glomerular filtration rate (GFR; by iohexol clearance) or the degree of GFR reduction at 4 weeks post-radioiodine treatment.[32] However, in that group of cats only, 5 of 21 progressed to renal dysfunction defined by increased serum creatinine concentration and decreased GFR, but none of the cats had increased BUN. We acknowledge the use of pre-treatment methimazole trials by some to screen for hyperthyroid "masked" renal disease,[28] but we had no data available, as this screening is not routinely used at the facility from which these data were garnered.

There are four groups in the current study defined by selected aspects of their medical management (eg pre-treatment methimazole exposure and/or concurrent cardiac medications and no medications). These groups were defined retrospectively from the available data, not by prospective design. These groups were analyzed to determine if there were any difference in the biochemical status among the groups, suggesting medical management affected the group's biochemical parameters. No differences were found except the relative degree of T4 change as mentioned above.

## CONCLUSION

There are a number of shortcomings to our approach, but our data is a sample of what is encountered in a stand-alone feline hyperthyroid treatment facility, acknowledging that some cats in severely debilitated states were not referred for or considered for treatment of their hyperthyroidism. For example, we had no data on the time of day in which the T4 samples were obtained for either the pre-treatment or post-treatment samples. Because there is some fluctuation in T4 values with time, this could have influenced our analysis using single samples before and after treatment. We acknowledge that all drug-related variables including dose, duration, and owner compliance were not documented. Because we had no control over those variables, we chose not to quantitate them out of concern for overstating the data. We also acknowledge the shortcoming of grouping cats treated with beta-adrenergic blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors individually or in any combination into one cardiac medication group, because the physiologic effects of the individual drugs are different. However, the goal was only to determine if cats considered sufficiently ill to justify any kind of pharmacologic heart management exhibited any

different pre-treatment or post-treatment serum biochemical trends compared to those exposed to methimazole or to those without any management drugs. Finally, we acknowledge that the interpretation of the biochemical values, heart rate, and the clinical status of the cat may have influenced the cardiac medication decisions both at the primary care facility pre-treatment and at the treatment facility.[8]

Based on our data and that from previous reports, we suggest caution in counseling clients with severely hyperthyroid cats to manage expectations. In this report, the terms "significant" and "statistically significant" are used in the mathematical sense, but these should not be unequivocally equated to clinical relevance. Earlier reports suggest that among hyperthyroid cats, 69% have biochemical evidence of pre-existing liver disease and 14% have evidence of pre-existing renal disease, but that older cats survive longer post-treatment and those treated with radioiodine survive longer than those treated with methimazole.[12] To us, this in combination with our own experience suggests that some risks (eg, treatment in the face of pre-treatment BUN or creatinine concentrations less than 2x or 1.5x upper normal limits, respectively; treatment in the face of pre-treatment ALT concentrations 2.5x upper normal limits) are justified in making the radioiodine treatment decision, but we acknowledge disagreement exists.

**Conflict of Interest**

None of the authors have any financial or personal relationships that would inappropriately influence their work.

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