

## RESEARCH ARTICLE

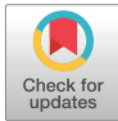
# A retrospective evaluation of the relationship between symmetric dimethylarginine, creatinine and body weight in hyperthyroid cats

Donald Szlosek<sup>1</sup>, Jane Robertson<sup>1</sup>, Jessica Quimby<sup>2</sup>, Rebekah Mack<sup>1</sup>, Jennifer Ogeer<sup>1a</sup>, Celeste Clements<sup>1</sup>, Donald J. McCrann<sup>1</sup>, Michael J. Coyne<sup>1\*</sup>

**1** IDEXX Laboratories, Inc., Westbrook, Maine, United States of America, **2** Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, Ohio, United States of America

▫ Current address: Antech Diagnostics, Fountain Valley, California, United States of America

\* [michael-coyne@idexx.com](mailto:michael-coyne@idexx.com)



## Introduction

- Hyperthyroid prevalence of 6-10% of cats >10yr
- Reported incidence of CKD 15-49% of Hyperthyroid cats
- Hypermetabolic state caused by hyperthyroidism leads to increased GFR and reduced muscle mass, often confounding the diagnosis of CKD – these pathological changes complicate finding a reliable and consistent marker for renal dysfunction prior to or at the onset of treatment for hyperthyroidism and may influence the long term management of hyperthyroidism as well as influence renal health
- Crea has been the most common renal biomarker used in the diagnosis and monitoring of renal dysfunction in cats
- Loss of muscle mass results in decreased crea – leads to difficulty interpreting crea in hyperthyroid cats due to the degree of muscle wasting often present
- Crea can remain within the normal ref range in some cats with hyperthyroidism despite concurrent renal disease
- Symmetric dimethylarginine (SDMA) has been shown to be an earlier and more sensitive biomarker for assessment of GFR and the evaluation of CKD in feline and canine patients
- SDMA is a by-product of intranuclear arginine methylation and is excreted primarily (greater than 90%) by renal clearance
- Because SDMA is excreted by the kidneys, serum concentrations are affected by changes in GFR, however unlike crea are not impacted by lean body mass
- Because SDMA is unaffected by lean body mass it is hypothesized that SDMA would be a consistent indicatory of kidney function in hyperthyroid cats undergoing treatment for hyperthyroidism

## Aim

- To use big data to describe the relationship between CREA and TT4, SDMA and TT4 and the changes observed in body weight, SDMA, and crea during treatment of feline hyperthyroidism.
- Second aim was to demonstrate the feasibility and utility of a data collection method referred to as big data

- Big data uses statistical methods to take a large population with low information density and create interpretable data to better understand the relationships and dependencies within the populations and perform predications of outcomes and behaviours. By aggregating large amounts of data and accounting for the multitude of inputs and layers a better picture of what constitutes a disease, trend or result interpretation for an entire population can be developed

## Material and methods

- Data from idexx US ref lab from clinical cases
- 453,126 individual cats – inclusion criteria TT4, SDMA, crea measured at least once in single blood sample
- Hyperthyroid cat group was identified from this sample population
  - inclusion into hyperthyroid 6-25yrs of age
  - had to have at least a single blood sample with a TT4 conc that was greater than 4.7ug/dl (upper limit of idexx ref range) along with a SDMA and crea , body wt obtained when available
- Hyperthyroid treated grp was identified from the hyperthyroid cat group
  - inclusion – hyperthyroid cats has to have sample from more than once visit in which the TT4, SDMA and crea were measured and demonstrated a change in TT4 conc in those samples using the following criteria on the sample from the first visit following their maximal TT4 conc (>4.7ug/dl) the conc of TT4 has to have decreased by a min of 2.5ug/dl and be  $\leq 4.7$ ug/dl .
  - Treatment was defined in this manner seen as treatment given was not known in each patient.
  - The pre-treatment visit was defined as the first time at which the cats sample had a TT4 > 4.7 ug/dL .
  - The post treatment visits were defined as all subsequent visits where the cat's sample had a TT4 conc of  $\leq 4.7$  ug/dL with a minimum decrease of 2.5ug/dL from pre-treatment period was limited to 120 days.
  - Cats with samples that remained hyperthyroid (TT4>4.7 ug/dL) during the post treatment visits were excluded
- A control grp was identified from the baseline feline population of 453,126 cats.
- For inclusion in the euthyroid control grp cats has to have samples for at least one visit in which the TT4, SDMA and crea were measured and have a TT4 conc  $\geq 0.8$ ug/dL and <2.3ug/dL on all visits
- Control cats with bodyweight information were selected at 10:1 age matched comparison with the hyperthyroid treated population that has complete body weight information
- The time (measured in days) from pre-treatment to post treatment visits was separated into 30 day increments to reflect clinical follow up times
- The beginning of the post treatment time periods was done pre-hoc and blinded to the results of the response
- If a cat has more than one visit in a defined 30 day increment the latest was used.

- These time periods (1-30days, 31-60 days , 61-90 days and 91-120 days ) were used as timepoint comparisons for changes in BW, SDMA, and crea
- Pre-treatment population was compared to all time points and each time point to each other to determine if any significant changes were present in BW, SDMA and crea during treatment

### **Biomarkers**

- Crea, SDMA and TT4 conc were determined at Idexx ref lab on Beckman AU clinical chemistry analysers
- SDMA was determined using a commercially available high – throughput immunoassay (IDEXX SDMA TEST)
- CREA was determined by a colorimetric method, Jaffe’s reaction using picrate at alkaline pH
- Total T4 was determined by automated enzyme immunoassay (EIA) method to measure serum TT4 (DRI T4 assay)
- Ref intervals for SDAM (0-14 ug/dL), CREA (0.9-2.3 ug/dl) and TT4 (0.8-4.7 ug/dL) in adult cats were previously established according to clinical lab and standards Institute (CLSI) guidelines

### **Results**

- 23,431 cats made up the hyperthyroid cat group with at least one visit where the cat had a TT4 value >4.7 ug/dL
- From the hyperthyroid population 4,680 cats met the criteria to be included in the hyperthyroid treated group population
- Median age at the pre treatment visit was 14 years (range 6-24 years)
- Domestic cats (DSH, DMH, DLH) 82% of the hyperthyroid treated group other most common breeds Siamese, American shorthair, Maine coon , Abyssinian 5%
- Only 2,804 cats had body wt recorded
- SDMA and CREA were compared to TT4 conc for the entire study group (n=113,535)
- A negative relationship was found between CREA and TT4 conc
- No relationship was found between SDMA and TT4 conc
- Association between hyperthyroid and body weight
  - 1,281 (27.4%) of hyperthyroid cats had body weight available for their pre-treatment visit
  - There was no statistically significant difference between the distribution of SDMA and crea, and age between the cats that has their body weight recorded when compared to those cats that did not
  - When a comparison of body weights of control euthyroid cats to hyperthyroid cats was performed cats with hyperthyroid weighed less than control cats
  - Similarly cats with hyperthyroidism had lower conc of both crea, SDMA compared to control euthyroid cats
  - Crea and SDMA conc, body weight increased significantly between the pre-treatment hyperthyroid and 30 days post treatment visit
  - Crea conc were significantly lower at the 1-30 day post treatment visit compared to the control cats
  - SDMA conc at the 1-30 day post treatment visit were not statistically different from controls
  - Hyperthyroid cats had significantly lower body wt pre-treatment and at 1-30 days and 31-60 days versus 91-120 days

- Hyperthyroid cats had significantly lower crea conc pre-treatment and at 1-30 days, 31-60 days vs 91-120 days
- Pre-treatment SDMA conc were significantly lower in comparison to all post treatment time points
- However after the initial increase in SDMA conc at 1-30 days , there was no significant difference in SDMA conc throughout the remainder of the treatment periods

## Discussion

- Increased TT4 conc correlated with a decrease in CREA conc – consistent with previous observation that kidney dysfunction may be masked by the hypermetabolic state of hyperthyroidism and reduced muscle mass results in reduced production of CREA
- Contrast SDMA conc did not significantly decrease with increasing conc of TT4, suggestion that SDMA is more resistant to the effect of reduced muscle mass and increased GFR associated with increased TT4 conc than is CREA
- A recent study on thyroidectomised hyperthyroid cats suggested a weak correlation between SDMA, body wt and TT4 levels
- In contrast when pre-treatment cats were compared to control cats in the present study populations only pre-treatment cats has a significantly lower SDMA and at no other time point was the SDMA conc lower than the control population conc
  - This finding implies that if increased protein turnover resulting in increased SDMA production is occurring it may be relatively small effect
- It has been well established that the hyperthyroid state in cats causes an upregulation of GFR or hyperinflation - several previous studies suggest that as treatment is initiated regardless of type, this upregulation of GFR is corrected around 30 days
- In this study SDMA did increase significantly between pre-treatment and 1-30 days in the treated population
  - represents a correction of hyperfiltration and correlates with an expected normalization in GFR after treatment
- The lack of significant difference between the SDMA conc at 1-30 days and the rest of the time periods likely reflects how minimal the effects of extrarenal factors may be on SDMA esp those of such as muscle wasting and subsequent weight gain during treatment of the hyperthyroid state
- 1.5kg weight difference was demonstrated between the euthyroid control cats and pred-treatment visit hyperthyroid cats with recorded body weight
  - on average representing at 27% reduction in body mass in the hyperthyroid population versus their age matched counterparts
  - It is likely that a portion of this weight loss is due to reduced muscle mass , as thyrotoxicosis causes loss of muscle mass in the feline patient and is hallmark of hyperthyroidism affecting over 75% of patients
- Significant increase in body weights were seen subsequent to tx, demonstrating that the study population appears to align with the known changes in muscle mass during therapy for hyperthyroidism
- Cat body weight increased in weight by 0.4kg by months post tx
- Both crea and SDMA conc increased in the initial 1-30 day time period.

- BUT only crea conc continued to increase for months after GFR should have stabilized. This supports the conclusion that changes in muscle mass continued to affect crea levels even 3 months post initiation of therapy for hyperthyroidism
- Peterson et al demonstrated that a small % (10%) of appropriately treated cats remained thin but almost half remained muscle wasted and even in cats with follow up exceeding 6 months, muscle wasting was still present.
- Crea conc therefore may remain an inadequate measure of renal function beyond the achievement of euthyroid status
- Limitations
  - incomplete results for some parameters, irregular timepoints , potential bias toward, irregular timepoints, potential bias for sick patients , no BCS, MCS< or BMI were not available and body weight was used as a proxy for lean body mass , only 98 cats has a follow up time point at the 91-120 day time period – thus survivorship bias, no USG was included in results and those cats with confirmed CKD were not identified

## Conclusion

- Findings suggest that crea conc significantly decreased with increasing conc of TT4, whereas SDMA did not
- In cats treated for hyperthyroidism both crea and SDMA conc increased in the immediate post treatment period which is an indication of resolution of hyperinflation and reduction in GFR
- After this initial increase post tx SDMA conc remained stable during the post Tx period, crea conc however continued to increase throughout the extended post-treatment period supporting the argument that the extrarenal factors such as muscle mass influence crea in this disease state
- This study supports that SDMA is less affected by extrarenal factors than crea in hyperthyroid cats before and after treatment

Received: 15 March 2020 | Accepted: 22 May 2020

DOI: 10.1111/jvim.15831





**STANDARD ARTICLE**

Journal of Veterinary Internal Medicine

**ACVIM**  
American College of  
Veterinary Internal Medicine

Open Access

# Assessment of serum symmetric dimethylarginine and creatinine concentrations in hyperthyroid cats before and after a fixed dose of orally administered radioiodine

Lucia Yu<sup>1</sup>  | Lauren Lacordia<sup>1</sup>  | Sue Finch<sup>2</sup>  | Thurid Johnstone<sup>1</sup> 

## Introduction

- 10-49% of cats with hyperthyroidism have concurrent renal azotaemia diagnosed before or after treatment

- Increase in thyroid hormone production in hyperthyroidism increases renal blood flow and glomerular capillary hydrostatic pressure thereby increasing GFR
- Indirect measurements of GFR such as serum crea and urea nitrogen conc are notoriously inaccurate at detecting CKD in hyperthyroid cats
- Their inaccuracy is largely attributed to the effects of extrarenal factors such as muscle mass as well as daily variability in exogenous and endogenous protein loads
- Pre-treatment GFR has been proposed as a potential predictor of post treatment azotaemia
- SDMA is an indirect biomarker of GFR that is unaffected by muscle mass and reportedly detects CKD with higher sensitivity than creatinine

## Aim

- Prospectively measure serum SDMA conc in hyperthyroid cats receiving a fixed PO dose of radioiodine before and after treatment and to assess serum SDMA conc in relation to serum crea and TT4 conc at both time points
- It was hypothesized that serum SDMA conc would increase significantly as hyperthyroidism resolves
- Serum SDMA and crea conc were expected to be significantly correlated only after hyperthyroidism resolved, leaving fewer extrarenal factors to affect serum creatinine conc
- After radioiodine treatment where renal dysfunction was suspected based on serum conc and concurrent suboptimal USG, serum SDMA conc was hypothesized to be concurrently increased

## Materials and Methods

- Hyperthyroid cats and cats that were deemed appropriate for treatment with a fixed dose of radioiodine (138 Mbq 3.7mCi) PO
- Inclusion and exclusion criteria of a previously established standard radioiodine treatment protocol
- Eligible for treatment with fixed dose radiation after a definitive diagnosis of hyperthyroidism was made based on presence of clinical signs consistent with polyuria, unkempt coat and serum TT4 conc above the upper limit of ref interval
- Data
  - Age, sex and neuter status were recorded for each cat at the initial (T0) presentation and at least 3 months (T1) after radioiodine treatment
  - PEx – BP , bwt, BCS, MCS (9 and 4 point scale respectively)
  - Blood and urine were sampled at T0 and T1
- Defining kidney dysfunction
  - Renal azotaemia was defined as a serum crea conc of  $\geq 1.6$  mg/dL ( $\geq 140$   $\mu$ mol/L) or a serum SDMA conc of  $\geq 18$   $\mu$ g/dL with concurrent USG  $< 1.035$
  - The severity of kidney dysfunction then was stratified separately into CKD stages based on serum creatine and SDMA conc according to IRIS CKD staging guidelines
  - Where urine conc was  $\geq 1.035$  prerenal azotaemia was defined as a concurrent serum crea conc  $\geq 1.6$  mg/dl ( $\geq 140$   $\mu$ mol/L) or serum SDMA conc  $\geq 14$   $\mu$ g/dL
  - Possible IRIS stage 1 CKD was defined by documenting a single USG  $< 1.035$  with a concurrent serum crea conc  $< 1.6$  mg/dL ( $< 140$   $\mu$ mol/L) or serum SDMA conc  $< 18$   $\mu$ g/dL

## Results

- Sample Characteristics
  - 76 cats were required for the study to sufficient power to detect a difference between SDMA and creatinine for detection of CKD at T1
  - Drop out rate of up to 40% was expected and thus in the 108 cats were enrolled
  - 28 (26%) did not complete the study or were excluded
  - 80 (74%) cats returned for their T1 evaluation and were included in this study
  - Then median duration from treatment to re-valuation was 108 days
  - 70 DSH , 5 DMH/DLH, 2 Ragdolls and 1 Tonkinese and Burmese
  - 47 (59%) FS, 33 (41%) MN cats
  - Median age was 12.9 years
  - T0 17 cats had serum TT4 conc >15.0 ug/dL (>193.0 nmol/L)
  - At T1 2 cats had persistent hyperthyroidism based on serum TT4 conc above upper limit of the reference interval
  - 66 cats (82.5%) cats had serum TT4 conc within the ref interval and 12 (15%) cats had serum TT4 conc below the lower limit of the ref interval
  - At T0 26 cats (33%) received IM sedation before urine and blood sampling whereas 3 cats received IM sedation at T1
- Renal clinicopathological parameters before and after radioiodine treatment
  - SDMA conc increased in 52 of 75 cats (69%) decreased in 21 (28%) cats and was unchanged in 2 (3%) cats from T0 to T1
  - Of the 21 cats with serum SDMA conc decreased between T0 and T1 , 18 cats had a concurrent increase in TP conc
  - 16 cats were euthyroid and 5 had serum tt4 conc below the lower limit of the ref interval
  - The 2 cats with unchanged SDMA conc at T0 and T1 were both euthyroid T1
  - Serum creatinine conc increased in 78 of 80 (96%) of cats and decreased in 2 (3%) and was unchanged in 1 cat from T0 to T1
  - Those cats with decreased or static serum creatinine from T0 to T1 all were euthyroid at T1
  - Urine specific gravity decreased in 49/76 64% cats increase in 19 (25%) cats was unchanged in 8 (11%) cats from T0 from T1 ,
  - At T0 19/80 (24%) cats had USG <1.035 of which 1 was considered to have renal azotaemia
  - At T1 37/76 (49%) cats had USG <1.035 of which 26 (34%) were considered to have renal azotaemia
  - 80 cats PCV decreased and TP conc increase significantly at T1 compared to T0
  - A significant increase in the means of serum creatinine, urea and SDMA occurred, Whereas mean serum TT4 and USG decreased significantly in the total sample at T1
  - When only cats with serum TT4 conc within the ref interval (those euthyroid) at T1 were considered n=66 cats a significant increase in mean serum creatinine and urea and SDMA conc occurred in T0 to T1 , whereas re the mean USG decreased significantly from T0 to T1
  - In this group of cats 32 of 62 (51%) has USG <1.035 at T0. Five cats had USG <1.035 at both time points but remained non azotemic
  - Only 2 cats with USG <1.035 at T0 had an increase in USG to  $\geq 1.035$  at T1 , neither of these cats has a renal azotaemia based on serum creatinine conc at T0

- In the 12 cats with a serum TT4 conc below the lower limit of the ref interval at T1 mean serum SDMA conc were not significantly different between T0 and T1
- However mean serum conc for creatine and urea increased where mean USG decreased significantly from T0 to T1
- 5 of the 12 cats were considered to have renal azotaemia based on the serum creatinine conc and USG at T1 in which USG <1.035 has been present at T) in 2 or 5 cats
- IN the 2 cats that remained hyperthyroid at T1 both cats has USG  $\geq 1.035$ , with normal serum create conc at T0 and T1 . The serum SDMA conc were within the normal ref interval for both cats at T0 . At T1 the serum SDMA conc remained normal 1 cat and increased slightly above the ref interval in the other
- Categorization of renal dysfunction by SDMA or creatinine before and after radioiodine treatment
  - IRIS stages at T0 based on both serum creatinine and SDMA conc
  - Serum SDMA and creatinine conc agreed on IRIS CKD staging in 13 of 17 (76%) of cats with 12 possible IRIS stage 1 CKD and 1 with stge 2 CKD
  - Based on serum SDMA conc 4 cats were classified as having stage 2 CKD or higher , whereas only 1 cat was classified as having stage 2 CKD and non had higher stages based on serum crea
  - The number of cats with USG <1.035 was not large enough to perform valid statistical testing to assess concordance of categorisation of IRIS staging between serum SDMA And creatinine conc for this subgroup
  - Only 1 of 26 cats given IM sedation before blood and urine sampling had discordant staging between SDMA and crea at T0
  - Serum SDMA and creatinine conc agreed with IRIS CKD staging in 17 of 36 (47%) 8 with possible stage 1 CKD and 9 ith stage 2
  - Based on serum SDMA conc 13 cats were classified as having stage 2 CKD or higher wherea based on serum crea conc 26 cats were classified as having stage 2 CKD and non with higher stages
  - FOR all cats at T1 poor agreement of IRIS CDK staging was found when comparing classification by creatinine with SDMA
- Correlation between serum SDMA and creatinine before and after radioiodine treatment
  - Correlation between SDMA and crea at T0 and T1 was assessed in 77 cats
  - No significant correlation was found between serum SDMA and creatinine conc at T0 when the entire population was included
  - Moderate significant correlation was found between SDMA and crea at T1 when the entire sample was analysed
  - In the subgroups of cats with USG <1.035 and those with USG  $\geq 1.035$  at To and T1 there was non significant correlation between SDMA and crea at T0 but a moderate correlation was foun between SDMA and creatinine at T1
  - Multivariable analysis failed to identify any significant influence of extrarenal factors such as BCS and MCS on SDMA and crea at both T0 and T1
- Relationships among serum SDMA , creatinine and TT4 conc
  - No significant correlation was found between serum SDMA and TT4 conc at T0 and T1
  - A moderate and significant correlation was found between serum creatinine and TT4 conc before radioiodine treatment , this relationship weakened after treatment



## Discussion

- Mean SDMA conc increased significantly as hyperthyroidism resolved
- This is presumably because serum SDMA conc correlates with GFR and an increase in serum SDMA conc is expected as the effects of hyperthyroid on renal perfusion resolves
- However serum SDMA conc did not increase in 21 (28%) of 75 cats, 5 of which has serum TT4 conc below ref range at T1. In these cats the concurrent decrease in serum SDMA conc is particularly surprising because several of these cats may be hypothyroid and GFR is expected to decrease in app half of the cats with iatrogenic hypothyroidism
- Similar to previous studies SDMA and crea were not correlated before radioiodine treatment with only moderate correlation seen after treatment
- AT T0 76% of cats with USG <1.035 had agreement on possible IRIS stage 1 CKD based on both serum crea and SDMA (with SDMA classifying other 4 cats into higher IRIS staging) – suggesting higher sensitivity for renal dysfunction in SDMA
- However at T1 serum SDMA conc classified with cats <1.035 into both higher and lower IRIS stages than did serum crea conc
- This finding is inconsistent with the hypothesis that serum SDMA conc would always be increased in cats with suspected renal dysfunction (based on USG <1.035 with concurrently increase serum creatinine) after radioiodine treatment
- In contrast to SDMA serum crea conc increased in all but 2 cats at T1 compared with T0
- In support of our findings another study did not find a significant correlation between serum SDMA conc and GFR before or after radioiodine treatment, whereas serum creatinine conc and GFR correlated moderately and significantly
- Taken together these results suggest that SDMA lacks specificity for detecting renal dysfunction in hyperthyroid cats
- This finding contrasts findings of a previous study that reported a specificity of 97.7% for pretreatment SDMA in detecting masked CKD in untreated hyperthyroid cats
- The correlation between serum TT4 and SDMA conc were very weak at T0 and T1
- Propose that extrarenal factors influence SDMA in hyperthyroid cats
- SDMA in hyperthyroid cats sedation, BCS < MCS did not appear to influence the trend in serum SDMA or crea conc at either time point when assessed using multivariable analysis
- Dehydration may affect serum crea and SDMA however dehydration was not evident during physical examination or evaluation of total protein conc
- 86% of cats with decreasing serum SDMA conc between T0 and T1 had an increase in TP conc during that time
- Another study proposed that serum SDMA conc in hyperthyroid cats may be affected by alterations in protein metabolism and potential alterations in hepatic clearance in SDMA
- Upregulation of SDMA production also a possible reason but has only been reported in growing animals
- Genetic variation could contribute to interindividual variability in SDMA metabolism – in people a genetic variant of the AGXT2 gene have been linked to enhanced SDMA metabolism in vitro – has not been assessed in cats
- Renal azotaemia was more common in cats with serum TT4 conc below the lower limit of the reference interval after radioiodine treatment than in those with serum TT4 conc within the ref interval
- The chosen follow up time after radioiodine treatment was approximately 3 months
- Although the expected recovery time for atrophic thyroid tissue after resolution of hyperthyroid is 1-3 months in most cats

But recent evidence indicates a large proportion of cats could develop overt hypothyroidism as late as 6 to 12 months after radioiodine treatment with radioiodine

This could further influence renal function such that results of our study may not accurately reflect long term thyroid function

However most changes in renal function related to resolution of hyperthyroid occur in the first month after I131 tx with no further significant change in GFR between 1 and 6 months after treatment

Furthermore up to 30% of previously healthy , geriatric cats will develop CKD over the course of 12 months

Such occurrence could confound the interpretation of results if follow up periods after radiation treatment increase beyond 3 months

Limitations – did not define hypothyroid with further function testing , only 1 serum sample was used to define IRIS stage, used ref lab cut off

#### Summary

SDMA conc increased inconsistently after treatment suggesting that extrarenal factors affect serum SDMA conc in hyperthyroid cats

SDMA and crea conc cannot be substituted for each other and serum SDMA conc in hyperthyroid cats should not be interpreted in isolation , because they may not adequately reflect renal function in these cats

Received: 30 May 2018 | Accepted: 28 January 2019

DOI: 10.1111/jvim.15450

Journal of Veterinary Internal Medicine   
Open Access American College of  
Veterinary Internal Medicine

**STANDARD ARTICLE**

## Changes in thyroid and renal function after bilateral thyroidectomy in cats

Heather L. Covey<sup>1</sup>  | Yu-mei Chang<sup>2</sup>  | Jonathan Elliott<sup>3</sup> | Harriet M. Syme<sup>1</sup>

- 1 study shown that cats were both hypothyroid and azotemic after treatment had shorter survival than non azotemic hypothyroid cats
- 5 studies report recurrence rates for hyperthyroidism between 5% and 27% between 3 and 59 months after surgery
- The highest rate of recurrence rates was in unilateral surgery ,
- otherwise reported as 5-11% recurrence
- recurrence was identified at the surgical site , especially with intracapsular technique and ectopic foci
- assessment of renal function in geriatric cats with changing thyroid status poses many challenges
- after treatment of cats with RAI , GFR decreased after 1 month and did not decrease further at 6 months but creatinine increased for 3 months before stabilizing
- a possible explanation is increasing muscle mass ( and creatinine generation) in treated hyperthyroid cats

- in addition, thyroxine increases renal blood flow and GFR by RAAS activation, increased sympathetic nervous activity and decreased peripheral vascular resistance
- control of hyperthyroidism can therefore be expected to cause some increase in creatinine as GFR decreases
- SDMA correlates with GFR and crea
- Lean body mass had no effect on SDMA in contrast to crea and so SDMA may provide a useful indicator of renal function in cats before and after treatment for hyperthyroidism
- The first cross sectional study
- 1. Aimed to report the prevalence of hypothyroidism in cats in the first 6 months after bilateral thyroidectomy in first opinion practice
- 2. Longitudinal study aimed to report long term follow up of a subset of cats to determine if post surgical hypothyroidism is permanent or transient and the rate of recurrence of hyperthyroidism
- 3 all sample from both studies were analysed with the aim of assessing the influence of changing thyroid status on the relationship between SDMA and crea

### Materials and methods

- Inclusion – bilateral thyroidectomy performed as 1 procedure or 2 staged unilateral procedures and stored plasma for SDMA and TSH (and crea or TT4 if had not been measured previously)
- Inclusion in the cross-sectional study to determine the prevalence of hypothyroidism , required a single stored plasma sample, collected within 6 months of surgery, required additional samples to be available for at least 18 months after surgery
- Cats that developed recurrent hyperthyroidism were followed only up to the point that this developed, and the cat had additional treatment, usually with methimazole or carbimazole
- Cats were defined as hypothyroid if their TT<sub>4</sub> was below the ref rang <10 nmol/L with TSH above 0.15ng/ml concurrently
- Cats euthyroid had TT<sub>4</sub> within the ref range and TSH <0.15ng/mL
- Cats with plasma TT<sub>4</sub> above the lab ref range >55 nmol/L were considered hyperthyroid

### Results

#### 1

- 68 cats – all neutered and non pedigree , 41% male and 57% female , age 14.9 yr (9.3-20.4)
- Some cats were treated medically prior to sx
- Total T<sub>4</sub> measurement before surgery (within 2 months) was available for 45 cats and revealed that 24 cats were controlled t<sub>4</sub> <55 , 12 of which had low tt<sub>4</sub> on medication <10 , with 21 cats still hyperthyroid despite medication
- Thyroidectomy was performed as a staged process in 40 of 68 cats with a median intra-operative interval of 258 (16-2086) days
- In the first 6 months post surgery , hypothyroidism was documented in 33 or 68 (49%) of cats , 15/68 (22%) cats continuing to be hyperthyroid and 13/68 (19%) cats euthyroid
- The prevalence of overt hypothyroidism in the first 6 months was greater in cats that had both thyroid glands removed in a single surgical procedure (67.9%) compared with cats having staged thyroidectomies 40%

#### 2.

- 23 cats had long term follow up range 595-1955 days
- Of these cats 16 had low TT4 after sx and 7 cats had normal tt4
- 12 of the cats -75% with low TT4 initially had normalization of TT4 conc >10nmol/L and <55 nmol/L 234 (193-992 days) after surgery
- 50% of these cats had recurrence of hyperthyroidism
- In total 10/23 cats became hyperthyroid after bilateral thyroidectomy included 6 cat with a TT4 initially < 10nmol/L giving a longer term recurrence rate of hyperthyroidism post surgery of 43.5%
- 16 cats showed a pattern of TSH increase after surgery with a prolonged time between restoration of normal T4 and resolution of increased TSH conc
- The time for documentation of TT4 within ref range in all 23 cats was 412 days (range 21-1955 days) and for TSH to return to ref range was 552 days

3.

- SDMA and creatinine were linearly associated but the classification of renal status (azotemic/nonazotemic or normal/increased SDMA) was discordant in many cases
- SDMA was above ref range in 30% of samples where creatinine was within RI
- USG was available for 33/45 samples and 13% were USG >1.035
- 9% of the discordant samples were from hyperthyroid cats
- 5% of samples creatinine was increased with normal SDMA – USG was measured concurrently in 5 of the 8 of these cats with increased creatinine and normal SDMA and USG was <1.035 in all of the them – all 8 cats had concurrent TT4 conc within or below the ref range

## Discussion

- Recurrent hyperthyroidism occurs in 5-11% of cats after bilateral thyroidectomy as compared to recurrence in our pop of 22% in the short term within 6 months of surgery with a further 44% over the long term up to 1049 days
- Recurrence more frequent with intracapsular technique or in the presence of ectopic tissue
- These cats did not undergo presurgical screening (technetium scintigraphy) for ectopic tissue, estimated to affect 4-12% of cats or carcinoma estimated at 2 %
- The recurrence of hyperthyroidism after thyroidectomy is a concern for only 11.5% of owners seeking radioiodine treatment
- most cats 40/68 had staged procedures in some cases with a prolonged time between them – this is despite the presence of bilateral disease occurring in the majority of cats 62.9-66.1%
- the reason for staging is thought to be due to concerns for iatrogenic hypoparathyroidism and subsequent hypocalcaemia
- stage surgery does reduce the incidence of hypocalcaemia
- this study documents restoration of euthyroidism in 39% of cats after bilateral thyroidectomy, although 2/3 of these had previously been hypothyroid
- success rates in published literature 66-90% post surgery but difficult to compare as definition of euthyroidism different and follow up short
- comparison on figures with published follow-up from radioiodine treatment – suggests that cats treated surgically in first opinion practice have a higher incidence of recurrent or persistent hyperthyroidism compared to 1.5-9.5% but comparable rate of hypothyroidism (between 4-36%) depending on the study
- however our short term prevalence of hypothyroidism 49% is based on a single time point for each cat and so could have been too soon or too long after surgery to document cats with transient hypothyroidism or those for which the increase in TSH after surgery is delayed

- changes in thyroid status occurred at prolonged periods after surgery
- previous studies have mostly focused on follow up only in the initial 6-12 months post treatment but the present study suggests that longer term follow up of cats remains important
- thyroid function can and frequently does change dramatically at time periods far beyond 6 months for the whole population but in total 25/68 cats initially enrolled developed recurrent hyperthyroidism
- bias – long term follow up may be because those cats still demonstrating csx and thus had more frequent and longer visits, selection bias in those that have surgery may have been harder to control with medical therapy and those may be more prone to recurrence
- TSH declined rapidly to undetectable conc in hyperthyroid cats often preceding the development of hyperthyroidism by 6-12 months
- 7/9 cats with undetectable TSH progressed to hyperthyroidism with a further 1 having borderline thyroid status
- TSH suppression after radioiodine treatment in 7/8 cats in a previous study lasted <3 months and therefore the presence of persistent low TSH in this cat difficult to explain
- This variability in relationship of T4 and TSH may pose challenge when using TSH conc to characterise thyroid status after treatment for diagnosis of non thyroid illness, occult hyperthyroidism or subclinical hypothyroidism
- The findings of the present study impact upon the timing of decisions to initiate thyroid hormone supplementation, now a recommendation for all azotemic cats with low TT4
- Lack of suppression of TSH conc in cats with normal TT4 has been suggested to indicate subclinical hypothyroidism, therefore necessitating an increased dose of thyroid hormone
- In cats reported here TSH remained above ref range for prolonged periods after normalization of TT4. If this sustained increase in TSH were to be ascribed to occult hypothyroidism then some cats with normal T4 would also warrant supplementation – but all used different ref ranges for TSH thus hard to interpret but use of a broader range might be appropriate after treatment of hyperthyroid cats
- SDMA and crea had good correlation but 35% had discordant results
- SDMA was more often to increase with normal crea
- All cats with increased SDMA and crea within ref range were documented to have renal azotaemia (elevated crea and USG <1.035) at a previous time point
- However, 5% of samples in our population had increased crea (presumed to represent a reduced GFR) with SDMA in ref range
- This contrasts with a previous study that found the sensitivity of SDMA for a 30% reduction from median GFR to be consistently higher than that of creatinine
- Closer inspection of discordant samples with high crea and normal SDMA revealed USG <1.035 supporting presence of renal azotaemia – although the influence of prerenal factors in crea can't be discounted this suggests that SDMA could be misleading in some cats with renal azotaemia
- Assessment of SDMA and creatinine revealed a linear relationship.
- The GEE indicated that SDMA concentrations were related not only to creatinine concentrations but also to thyroid status.
- , SDMA was relatively higher in hyperthyroid cats' compared with euthyroid and hypothyroid cats.
- This is in contrast to the weak negative relationship of tT4 to both SDMA and creatinine found in a recent study



- This could be because of the effect of thyroid hormones on muscle mass with a resultant decrease in creatinine production.
- However, only bodyweight, and not BCS, was found to be significant.
- Alternatively, thyroid hormones alter cellular metabolism and protein turnover, and the effect of low thyroid hormone levels in reducing endogenous production of creatinine has been previously reported.
- Thyroid hormones might also have direct effects on SDMA generation, as demonstrated for cystatin C in hyperthyroid cats, and in humans, SDMA concentrations have been found to be increased with either hyperthyroidism or hypothyroidism.
- . The use of SDMA as a surrogate for GFR, therefore, has limitations, much as seen with the use of creatinine. It seems likely that thyroid status influences the concentrations of creatinine and SDMA, both relative to GFR and to 1 another.
- Unfortunately, for this retrospective study, gold standard assessment of renal function by GFR measurement was not available. Evaluation of BCS was recorded for only 92 of the 151 samples, and no record was made of muscle mass score. It is possible therefore that missing data could be the reason that there was an association with body-weight but not BCS.\
- In summary, after thyroidectomy, a high percentage of cats can develop recurrent hyperthyroidism.
- Cats can experience recovery of thyroid function, or progression to hyperthyroidism, for years after surgery. Cats that regained normal thyroid function often showed a lag phase, where TSH remained increased but tT4 had normalized.
- Conversely, when TSH is undetectably low, it is frequently, although not always, a harbinger of recurrent hyperthyroidism.
- Symmetric dimethylarginine and creatinine are strongly linearly related, as would be anticipated as they are both good estimates of GFR; however, they are also influenced by thyroid status.
- The association cannot be explained by changes in body weight or BCS. Further studies are required to evaluate the effect of hyperthyroidism on SDMA, ideally incorporating GFR estimation

Received: 14 August 2018 | Accepted: 29 November 2018  
DOI: 10.1111/jvim.15407

Journal of Veterinary Internal Medicine   
Open Access American College of Veterinary Internal Medicine

**STANDARD ARTICLE**

## Assessment of symmetric dimethylarginine as a biomarker of renal function in hyperthyroid cats treated with radioiodine

Eva Buresova<sup>1</sup>  | Emmelie Stock<sup>2</sup>  | Dominique Paepe<sup>1</sup> | Lisa Stammeleer<sup>1</sup> |  
Eva Vandermeulen<sup>2</sup> | Pascale Smets<sup>1</sup> | Luc Duchateau<sup>3</sup> | Herve P. Lefebvre<sup>4</sup> |  
Sylvie Daminet<sup>1</sup>

- Azotaemia is observed in 10% of hyperthyroid cats at diagnosis and 15-60% cats develop renal azotaemia after treatment
- SDMA is a by-product of protein methylation, is minimally protein bound, is freely filtered through the glomerulus
- In people more than 90% of SDMA is eliminated by renal clearance
- SDMA closely correlates with GFR in healthy elderly cats and cats with CKD

- Sensitivity and specificity of SDMA to identify decreased renal function in cats with CKD is 100% and 91 % respectively
- There is positive correlation of crea with lean body mass but no correlation of SDMA with lean body mass in healthy elderly cats suggesting that crea con cis more affected by age and lean body mass than SDMA
- SDMA has higher sensitivity to predict renal azotaemia than serum crea in hyperthyroid cats although sensitivity of SDMA is as low as 33%

## AIM

- Evaluate SDMA as a renal biomarker in hyperthyroid cats along with GFR and crea before and after 1 month I 131 tx

## MATERIALS AND METHOD

- Inclusion – dx of hyperthyroidism on CSx , increased serum TT4 and increased pertechnetate uptake in one or both thyroid glands or ectopic thyroid tissue on scintigraphy scan
- Exclusion – azotemia (crea >2.3mg/dL ) any clinically relevant systemic disease other than hyperthyroidism and use of any medication within 2 weeks before enrolling in the study except for antithyroid medication
- Antithyroid medication was stopped 10 days prior to I 131 tx
- Cats had to have consistent diet for at least 1 month before and during the study
- Raw meat diets excluded
- Cats were treated with an individually adapted dose of I 131 injected IV
- Dose was based on severity of cs , serum TT4 and thyroid to salivary gland ratio as determined on the pertechnetate scan
- T0 = 4-48 hr and T1 1 month before and after I131 tx
- T0 – hx, PEx, SBP , CBC, MBA, UA, U C&S , Abdominal US , standard 2 view thoracic rads , echo
- At T0 and T1 body weight (BW) , BCS< MCS, BP , serum TT4 , TSH , crea, urea, SDMA , GFR , USG , UPC ratio
- BP – doppler
- GFR
  - Exogenous plasma crea clearance testing was offered to owners and performed in 10/47 cats at T0 and T1
  - IV cath placed in cephalic vein , baseline blood sample obtained and 40mg/kg of crea injected IV , blood sample s collected 5, 30, 60,120, 180, 360 and 600 minutes
  - The clearance was equal to the dose divided by the area of the concentration versus time curve
  - The borderline low GFR cut value was defined as 1.9ml/min/kg and the low GFR cut off value as 1.4mL/min/kg based on previous data
- Thyroid status
  - One month after treatment with I131 cats were classified as euthyroid if serum TT4 con was normal or below RI (0.8-4.7 ug/dL) with normal serum TSH conc ( $\leq 0.3$ ng/ml) as hypothyroid if TT4 conc was below RI with increased serum TSH conc  $>0.03$ ng/mL or as sub clinically hypothyroid if serum TT4 conc was normal with increased serum TSH conc ( $>0.3$ ng/mL) and as hyperthyroid id serum TT4 was above RI with TSH  $<0.3$  ng/mL

## Results

- 47 cats
- Median age was 13 years (range 7-16 years)
- Bwt and BCS significantly improved after treatment ,
- MCS improved in 60% of cats , remained stable in 36% and worsened in 4% of cats after treatment
- Serum crea conc significantly increased 1 month after I 131 treatment compared to T0
- Serum crea increased in 94% f cats decreased in 4% of cats and remained unchanged in 1 cat 2% after treatment
- Despite significant increase in crea at T1 all 47 cats remained non azotemic during the study period
- Urea significantly increased after treatment
- There was no significant difference in SDMA at T0 and T1
- Serum SDMA increased in 40% of cats decreased in 49% of cats and remained unchanged in 11% of cats
- The correlation between crea and SDMA was low at both time points
- USG and UPC significantly decreased after tx
- TT $\ddot{S}$  was significantly lower and TSH was significantly higher at T1 compared to T0
- One month after I131 treatment 2% remained hyperthyroid , 87.5% were euthyroid , 6.5% were sub clinically hypothyroid and 2% in which serum TSH conc was missing and tt4 conc was below RI
- All sub clinically hypothyroid and hypothyroid cats had normal serum crea and SDMA at T0 and T1 and 2 cats had USG <1.035  
Serum TT4 and creatine showed moderate and significant negative correlation at T) and low and not significant negative correlation at T1
- Serum TT4 and SDMA showed low and not significant negative correlation at both time points
- Correlation between serum TSH and crea was low and not significant at T0 but moderate and significant at T1
- Correlation of serum TSH and SDMA was low and not significant at both time points
- There was no sign difference in crea and SDMA , urea , USG or BW between the grp of euthyroid carts and the grp of subclinical hypothyroid and hypothyroid cats
- GFR significantly decreased after treatment
- None of the cats had low or borderline low GFR before treatment
- Correlation between GFR and SDMA was low and not significant at both times whereas the correlation between GFR and crea was moderate and significant in both times

## Discussion

- Moderate correlation of crea with GFR and a low correlation of SDMA and GFR and with crea
- SDMA did not significantly change after treatment which is in contrast to significant increase of crea and significant decrease of GFR after treatment
- Furthermore mildly increased SDMA before treatment normalized in some cats post tx
- Although based on low numbers serum crea and SDMA before treatment did not predict abnormally low GFR after treatment
- The correlations of SDMA and GFR and SDMA with crea were low and not significant at both times T) and T1
- This is in contrast to high and significant correlation of SDMA and GFR and SDMA with crea in previous studies



- Although GFR significantly decreased after treatment in all 10 cats there was no obvious pattern of SDMA changes in our complete study population
- This confirms the poor correlation of GFR with SDMA in our hyperthyroid cats
- As expected GFR and crea correlation in our population was only moderate because crea is known to be a poor renal marker in hyperthyroid cats
- Data of subgroup of cats in which GFR was measured show that neither serum crea nor SDMA perform well as renal biomarkers in hyperthyroid cats
- Glomerular hyperfiltration in hyperthyroidism leads to increased GFR which may influence also renal filtration of SDMA
- This could explain why SDMA before treatment did not predict low GFR after treatment
- Serum SDMA sensitivity (33.3%) to predict azotaemia after treatment of hyperthyroidism in cats is higher than crea sensitivity (11.9%) but these results indicate that SDMA is still a poor predictor of after treatment azotaemia
- There is a positive association of SDMA with increased thyroid function in humans
- Serum SDMA is a byproduct of protein methylation and protein metabolism is considerably changed in hyperthyroid cat
- Therefore we can speculate that hyperthyroidism might influence SDMA conc in cats
- The production rate of SDMA in the body is relatively stable but protein breakdown could potentially contribute to changes in serum conc
- SDMA is freely filtered by the kidneys but there is also hepatic clearance in people – unknown in cats \
- But weak to no correlation of SDMA and TT4
- Crea and urea significantly increased and GFR significantly decreased after tx of hypert
- But no cats became azotemic after treatment which is in contrast to the reported 15-60% of hypert cats become azotemic after tx . This study preselected for cats that were non azotemic and these cats were already on antithyroid meds so could affect post tx results
- Increase in crea may have been hampered by incomplete resolution of muscle mass loss at 1 month post tx but based on previous research that demonstrates renal function stabilizes after 4 weeks post treatment
- This reasoning is further supported by another study showing that GFR significantly decreases after 1 month of I131 tx but there is no further significant decrease in GFR between 1 and 6 months post treatment
- Long term follow up could show development of CKD unrelated to resolution of hyperthyroidism
- UPC significantly decreased after tx – this is an expected evolution as glomerular hyperfiltration changes in glomerular barrier as well as changes in tubular protein management increase proteinuria in hyperthyroidism and proteinuria decreased quickly after resolution of hyperthyroidism in people
- USG significantly decreased after treatment and more cats had USG <1.035 at T1 than at T0
- Hyperthyroidism can lead to crease ability to conc urine without clinical significance
- Serum creatinine was significantly higher in cats with none to mild muscle mass loss compared to cats with moderate to severe muscle mass loss before treatment but this difference was insignificant after treatment
- These results are in agreement with fact that crea is influence by muscle mass and crea might be lower in cats with muscle wasting such as cats with hyperthyroidism or CKD as well as elderly cats
- There was no significant diff in SDMA in cats with none to mild muscle mass loss when compared to cats with moderate to severe muscle mass loss

- % of hypothyroidism and transient hypothyroidism after I131 tx vary in literature from 5% incidence in older studies to 39%, 79% and 83% in later studies
- There is a lower incidence of hypothyroidism with low dose compared to standard dose 2 vs 4 mCi I131 with no signif diff of persistent hyperthyroidism between grps
- Despite using mean I dose of 142.6 MBq the incidence of hypothyroidism was low 9%
- This might be because of short term follow up and considering that iatrogenic hypothyroidism might develop up to 6-12 months later

### **Conclusion**

- Careful interpretation of mildly increased SDMA with normal crea in hyperthyroid cats is warranted considering that SDMA conc might return back to RI after resolution of hyperthyroidism in some cats
- Study shows lower correlation between SDMA and GFR compared to correlation between crea and GFR in hyperthyroid cats treated with I131