



Impact of radioiodine treatment on acute phase proteins in hyperthyroid cats

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Abstract

Objectives The aim of this study was to investigate the impact of radioiodine treatment (RIT) on the acute phase proteins (APPs) serum amyloid A (SAA), alpha-1-acid glycoprotein (AGP) and haptoglobin (Hp) in hyperthyroid cats.

Methods Between June 2013 and November 2014, 33 hyperthyroid cats without clinical or laboratory signs of inflammatory or neoplastic disease and a body weight >2.5 kg were enrolled. Immediately before, and 12, 36, 72 h and 6 days after RIT, serum samples were obtained for determination of APP concentrations.

Results Both SAA and AGP concentrations changed significantly after RIT. The concentration of AGP increased gradually after treatment with a maximum concentration at the end of the study period (median baseline 398 µg/ml; median 6 days post-RIT 562 µg/ml [$P=0.001$]). A relevant >two-fold increase in AGP was seen in 8/33 (24%) cats. SAA concentration increased significantly within 12 h (baseline 9.2 µg/ml; 12 h post-RIT 22.5 µg/ml [$P=0.012$]). In 7/33 (21%) cats, a clinically relevant >10-fold increase in SAA was observed. Hp concentration showed no significant change ($P=0.12$).

Conclusions and relevance RIT induced a mild, mainly not clinically relevant acute phase reaction (APR). AGP and SAA were useful APPs to determine RIT-induced APR.

Keywords: Acute phase reaction; serum amyloid A; alpha-1-acid glycoprotein; endocrine

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Introduction

Hyperthyroidism is the most common endocrine disorder in cats and radioiodine therapy (RIT) is considered the gold standard treatment. In humans and cats, RIT induces pyknosis and acute necrosis of thyroid cells and therefore leads to impaired cell replication, chronic inflammation and fibrosis.^{1,2} Radiation-induced destruction of thyroid tissue is reflected by a significant increase in proinflammatory, as well as anti-inflammatory, cytokines (interleukin [IL]-6, IL-10, tumour necrosis factor- α , interferon- γ) in people.^{3,4} Moreover, C-reactive protein (CRP), a major acute phase protein (APP) in people, shows a significant increase 1 week after RIT.⁵ However, even hyperthyroidism itself is associated with a prothrombotic state and an increase in proinflammatory proteins.⁶ The cause is believed to be an increased production of procoagulant and proinflammatory proteins.^{7,8}

In hyperthyroid cats, information about the behaviour of APPs is scarce. A few reports suggest that hyperthyroidism might also be associated with an acute phase

reaction (APR),^{9,10} and that the behaviour of APPs in endocrine disorders might be different to that of other diseases.¹¹

Each animal species is known to have its own specific APR, and also different major and moderate APPs, that is, proteins showing a more than a 10–100-fold and 2–10-fold increase, respectively.¹² In the cat, serum amyloid A (SAA) is a major APP, while alpha (α)-1-acid glycoprotein (AGP) and haptoglobin (Hp) are considered to be moderate APPs by some investigators.^{12,13} Others report AGP to

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be a major acute phase reactant in cats.¹⁴ The discrepancy between different studies might be due to the fact that not only the species, but also the underlying disease, might influence the behaviour of APPs during APR and thus their diagnostic utility. Moreover, there is evidence that age and sex potentially influence APPs (eg, SAA tends to be higher in older and in female cats).¹⁵ Also, the classification of major, moderate or minor APPs depends on the magnitude of the increases according to some classification systems, on the frequency of increase in each single species according to other systems and on the rapidity of the increase according to others.

To our knowledge, the behaviour of APPs following RIT in hyperthyroid cats has not yet been characterised. The knowledge of a typical APR after RIT is important for early recognition of changes in APP concentrations not solely attributable to the treatment, which might be suggestive of the presence of a concurrent disease. Thus, the aim of this study was to investigate the impact of RIT on the APPs SAA, AGP and Hp in hyperthyroid cats. A potential impact of sex on APP concentrations was assessed prior to RIT. The hypothesis was that, first, RIT induces a transient increase in APPs due to radiation-induced thyroiditis; secondly, SAA shows the highest increase and is thus the most suitable APP with which to detect an APR due to RIT in cats; and thirdly, there is an impact of sex on APPs prior to RIT.

Materials and methods

Study design and cats

In this prospective clinical study, hyperthyroid cats presented for RIT to the Clinic for Small Animals, Justus Liebig University Giessen between June 2013 and November 2014 were enrolled. The study was approved by the regional authority (Regierungspräsidium Giessen, No GI 18/17 35/2013).

Inclusion criteria were a diagnosis of hyperthyroidism confirmed by history, physical examination, increased total thyroxine (T4) concentration and/or abnormal thyroid scintigraphy. Medical treatment for hyperthyroidism was discontinued in all cats at least 1 week prior to RIT. Exclusion criteria were body weight <2.5 kg and a neoplastic or inflammatory disease other than neoplasia of the thyroid gland. Cats were also excluded if they did not tolerate the study procedures, or if they had received glucocorticoids or phenobarbital within 4 weeks prior to presentation, potentially influencing the results of thyroid hormones assessment or APR.

Work-up

Prior to RIT, complete physical examination, thoracic radiographs, echocardiography, electrocardiography, blood pressure, complete blood cell count (CBC), serum biochemical examination, measurement of total T4 and

^{99m}technetium-pertechnetate thyroid scintigraphy were performed in all cats. Urinalysis was carried out if the history or physical examination findings were suggestive of urinary tract infection. A follow-up CBC, biochemical examination and T4 measurement were performed on day 6 after RIT. Serum T4 concentration was measured by a commercial laboratory (Biocontrol, Ingelheim, Germany) using a chemiluminescent enzyme immunoassay.

Blood for the measurement of APPs was collected from a 22 G venous catheter placed prior to scintigraphy or by puncture of the vena cephalica antebrachii or vena saphena using a 20–22 G needle. Blood was collected into a plain tube, centrifuged within 30 mins of venepuncture and serum was stored at –80°C. APR prior to and 12 h, 36 h and 72 h, as well as 6 days after RIT was assessed by measurement of APPs.

Measurement of APPs

Serum samples were thawed at room temperature and mixed thoroughly. The samples were evaluated for the presence of haemolysis, icterus and lipaemia. Results obtained from severely haemolytic, lipaemic or icteric samples were excluded from statistical analysis.

SAA and Hp were measured on an automated analyser ABX Pentra 400 (ABX Pentra; ABX Horiba) using the reagents from the LZ test Eiken SAA (Eiken Chemical Co) and the Phase Range haptoglobin kit (second generation; Tridelta Development), respectively. Both assays have been previously evaluated for the measurement of APPs in cats.^{9,16–18} Before measurement of the study samples, a standard curve for both SAA and Hp was determined using calibration solutions provided by the manufacturer. For SAA concentrations below the lower limit of detection (LOD) of 0.38 µg/ml, left censoring was performed using the LOD/√2 approximation, resulting in a value of approximately 0.3 µg/ml.¹⁹ AGP was measured in duplicates using a commercially available species-specific ELISA for feline AGP (Life Diagnostics).²⁰

Reference intervals (RIs) used in this study were established by various methods. For Hp, the RI provided by the manufacturer of the test was used. For AGP, the maximum concentration detected in five healthy age-matched cats was used. For SAA, the one-sided RI was calculated based on 62 healthy blood donor cats (35 neutered male cats and 27 neutered female cats) presented between October 2017 and October 2018. The median age of the blood donor cats was 4 years (range 1–18). Using a robust method and commercially available software (MedCalc, version 19.2.2), the upper RI for SAA was 7.4 µg/ml. SAA concentration did not differ significantly in cats ≥8 years of age (n = 16, median 0.8 µg/ml [range 0.3–17.9]) and cats aged <8 years (n = 46, median 0.9 µg/ml [range 0.3–7.5]; *P* = 0.71).

The analytical performance of all APP tests used here is available in the supplementary material. For the major

APP SAA, an APR of clinical significance prior to RIT was defined as an SAA concentration exceeding 10-fold the upper RI (ie, 74 µg/ml). Following RIT, a >10-fold increase from initial values was considered a clinically relevant APR for SAA. For the moderate APPs AGP and Hp, a >two-fold increase from initial values was regarded as an APR of clinical significance.

RIT

In all cats ¹³¹iodine (I-131) was administered intravenously. Cats received a dose of I-131 ranging between 74 and 222 MBq based on the severity of clinical signs, T4 concentration and scintigraphic results.

Statistical analysis

Overall, 9/165 samples had to be excluded owing to severe haemolysis and 1/165 samples owing to severe lipaemia. In one cat, 4/5 AGP measurements were not possible owing to insufficient sample volume. In another cat, one implausible AGP result of '0' obtained at 36 h was excluded.

A Shapiro–Wilk test was used to assess normality. Data were not normally distributed and are presented as median (range). Owing to missing values, mixed-effects modelling with compound symmetry covariance was performed to evaluate the effect of time on APPs. In cases of significance, Fisher's least significance difference tests were used for post-hoc comparisons. Owing to non-normal data distribution, logarithmic transformation was performed in advance to fulfil the assumptions of the model. The potential influence of sex on APP concentrations prior to RIT and the impact of age on SAA concentrations in healthy cats was assessed with a Mann–Whitney U-test.

Statistical analysis was performed using commercial software (SPSS statistics, version 26 and Graph Pad Prism, version 6). The level of significance was set at $P \leq 0.05$.

Results

Out of 122 cats presented for RIT, 33 met the inclusion criteria. There were 27 (81.8%) domestic shorthairs, two Norwegian Forest Cats, two mixed-breed cats, one Ragdoll and one Turkish Van. The median age was 12 years (range 9–16) and median body weight was 3.9 kg (range 2.5–6). Fifteen cats were female (45.5%), 18 were male (54.5%) and all were neutered. Male cats had a median age of 11 years (range 9–16) and a median body weight of 3.9 kg (range 2.5–6). The median age and body weight of the female cats were 13 years (range 10–16) and 3.8 kg (range 2.6–4.8), respectively.

The median T4 concentration prior to RIT was 18 µg/dl (range 3.5–61). All but one cat had an increased T4 concentration (RI 1–4 µg/dl); a single cat had a T4 concentration of 3.5 µg/dl. This cat had a non-detectable thyroid-stimulating hormone concentration, and scintigraphy revealed two hot nodules confirming hyperthyroidism.

Prior to RIT, median T4 concentration was 20.7 µg/dl (range 7.5–61) in male cats and 12.1 µg/dl (range 3.5–36.9) in female cats. The median dose of I-131 administered in all cats was 185 MBq.

Echocardiography revealed moderate myocardial hypertrophy in 5/33 cats. Prior to RIT, clinical chemistry revealed a few changes typically seen in hyperthyroidism such as increased liver enzyme activities in 32 cats and mild hyperglycaemia in 18 cats (range 6.12–15.48 mmol/l; RI 3.89–6.11 mmol/l). In one cat mildly increased creatinine concentration (203 µmol/l; RI 0–168 µmol/l) and in nine cats mildly increased urea concentration (range 10.9–16.5 mmol/l; RI 3.3–10.7 mmol/l) were observed.

APP concentrations prior to RIT

APPs exceeded the upper limit of the RI (Figure 1) in the majority of cats. Of the 33 cats, 29 showed an increased AGP concentration, 18 an increased SAA concentration and in 11 an increased Hp concentration was observed.

Prior to RIT, median SAA, AGP and Hp concentrations were 9.2 µg/ml (range 0.3–162), 398 µg/ml (range 132–1477) and 1.7 mg/ml (range 0.1–2.4), respectively. In 2/33 (6%) cats, the initial SAA concentration exceeded 74 µg/ml. For more details on the APP concentrations of individual cats and their changes over time, see Table 1 (SAA), Table 2 (AGP) and Table 3 (Hp) in the supplementary material.

Sex did not have an impact on APP concentrations before RIT. Median SAA concentration was 12.6 µg/ml (range 0.3–118.6) in male and 6.6 µg/ml (range 0.3–162.1) in female cats ($P = 0.46$). Median AGP concentration was very similar in males (393 µg/ml [range 132–1477]) and females (409 µg/ml [range 165–1368]) ($P = 0.94$). This was also the case for the median Hp concentration: 1.8 mg/ml (range 1.0–2.3) in males and 1.6 mg/ml (range 0.1–2.4) in females ($P = 0.88$).

Impact of RIT on APP concentrations

Overall, RIT induced a significant increase in SAA ($P = 0.001$) and AGP ($P = 0.001$) concentrations, while it did not have a significant impact on Hp concentration ($P = 0.12$) (Figure 1). As seen in Figure 1a, median baseline SAA concentration (9.2 µg/ml) increased 2.4-fold after RIT with a peak after 12 h (median 22.5 µg/ml; $P = 0.012$) before decreasing again at 36 h (median 14.8 µg/ml). Six days after RIT, SAA concentration further decreased to 0.5 times the baseline concentration (median 4.2 µg/ml). At 12 h, SAA >74 µg/ml was observed in 9/33 (27%) cats. When compared with initial SAA results, a more than 10-fold increase was seen in 7/33 cats, consistent with a clinically relevant APR following RIT.

As seen in Figure 1b, median AGP concentration also increased significantly after RIT ($P = 0.001$), reaching the highest median concentration after 6 days (median 0 h: 398 µg/ml; 12 h: 473 µg/ml; 36 h: 526 µg/ml; 72 h: 542 µg/ml; 6 days: 562 µg/ml). This is consistent with

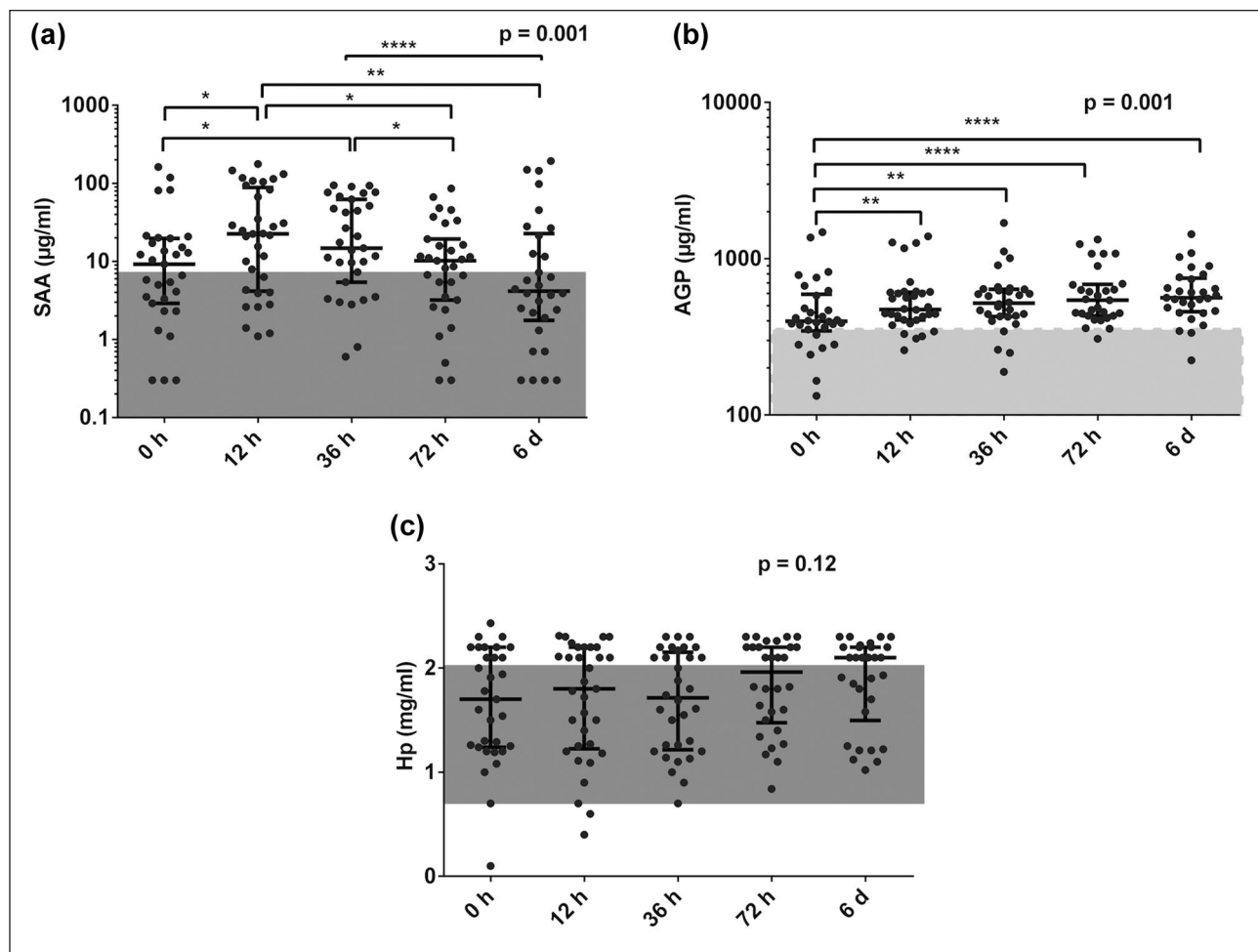


Figure 1 Concentration of (a) serum amyloid A (SAA), (b) alpha-1-acid glycoprotein (AGP) and (c) haptoglobin (Hp) before (0h) and 12h, 36h, 72h and 6 days after radioiodine therapy. Each measurement is shown as a dot; the central horizontal line indicates the median; the other horizontal lines are consistent with the 25th and 75th percentiles. Reference intervals for (a) and (c) are given in dark grey; for (b) the upper light grey bound is defined as the maximum of healthy cats; the area is marked in light grey owing to the preliminary nature of the upper limit of AGP in healthy cats. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$

a 1.4–1.5-fold increase in AGP concentrations 6 days after RIT, compared with initial concentrations. Overall, in 8/33 cats (24%), a >two-fold increase in AGP was observed following RIT. For detailed information about the behaviour of APPs in individual cats, see Tables 1–3 in the supplementary material.

Discussion

To our knowledge, this is the first study to evaluate the APR in hyperthyroid cats following RIT. We demonstrated that the concentration of APPs is increased even prior to RIT and that the APR is transiently augmented after treatment with I-131.

Although the knowledge in cats is limited, a systemic inflammatory reaction associated with a hyperthyroid state has been well described in humans. In hyperthyroid human patients, increased fibrinogen concentrations and

erythrocyte sedimentation rates (ESRs) suggestive of an inflammatory reaction have been reported.^{21–23} Moreover, fibrinogen correlates with T4 concentrations in hyperthyroid patients.²³ Experimental work on human hepatoma cells showed increased synthesis of fibrinogen and Hp concentrations after the injection of triiodothyronine.⁸ However, a systemic inflammatory response associated with hyperthyroidism in humans is not equally reflected by all acute phase reactants. While an increase in fibrinogen concentration was reported in several studies, Hp concentration, the ESR and CRP (a major acute phase reactant in humans) were not significantly different between hyperthyroid and euthyroid patients.^{24–28} The same appears to be true for cats. As demonstrated here, hyperthyroidism induced an increase in AGP concentration and, to a lesser extent, in SAA and Hp concentrations. Other investigators describing APPs reported an

increased SAA concentration in 2/4, 3/7 and 1/5 hyperthyroid cats, respectively.^{9–11}

Whether increased SAA concentration is an effect of hyperthyroidism or unrecognised comorbidities in hyperthyroid cats is unclear. The interpretation of these data is hampered by the lack of a healthy age-matched control group so that the sole impact of hyperthyroidism on APR cannot be distinguished from the impact of age or comorbidities potentially present in senior cats. However, factors such as visceral fat accumulation seen in obese cats are known to induce an APR characterised by an increase in the SAA concentration.²⁹ While hyperthyroidism is typically associated with a low body condition score, obesity might be a problem in euthyroid cats. Moreover, chronic kidney disease can result in increased APPs. In cats with kidney disease, 50 times higher mean SAA concentrations have been reported compared with healthy cats.³⁰ However, as only one cat had a mild increase in creatinine at the beginning of this study, it does not explain the APP concentrations seen prior to RIT. Nevertheless, increased renal blood flow during hyperthyroidism could have masked kidney disease prior to RIT and thus an influence on SAA concentration cannot be completely excluded.

All the factors mentioned so far might have had an impact on initial APP concentrations. As seen in human hyperthyroid patients, it seems that hyperthyroidism in cats can also lead to a mild, albeit detectable, APR.

Following RIT, both SAA and AGP increased as early as 12 h after I-131 administration. These changes indicate that the RIT induced a mild APR that was clinically significant in approximately 20–25% of cats. Overall, the cats showed a 2.5-fold increase in SAA concentration reaching a median of approximately 20 µg/dl that can be considered as mild APR. It is comparable to the degree of APR described in cats suffering from mild inflammatory diseases such as lymphadenitis or keratoconjunctivitis.¹¹ In contrast, SAA concentrations in cats showing a clinically relevant APR following RIT (>10-fold increase) were comparable to concentration levels seen in cats with severe acute inflammatory diseases such as acute pancreatitis or severe trauma.¹¹ However, despite the marked changes in laboratory results, major clinical signs were not observed in any of the cats. The most likely explanation is a radiation-induced thyroiditis as has been previously demonstrated in humans.^{5,22}

SAA concentration showed a rapid significant increase with a peak after 12 h and a decrease below baseline values after 6 days. This confirms that the measurement of the SAA concentration is useful as a diagnostic marker in the cat, reflecting the early phase of an APR with an increase within 1 day and a decrease within a few days.^{13,30} Peak SAA concentrations are seen around 24 h after a pathogenic stimulus. Owing to radiation safety measures, the SAA concentration was only evaluated 12 h

and 36 h after RIT. Thus, the peak concentration might have been missed.

In comparison with SAA, the concentrations of AGP remained increased throughout the study, when compared with initial results. AGP concentrations increased gradually, peaking towards the end of the study. Unfortunately, the test used here has not been used in clinical patients previously and only the manufacturer's data have been available for comparison with our results. A more commonly used method to measure feline AGP concentration,³¹ namely the single radial immunodiffusion, was no longer commercially available at the time of the study. This makes comparisons with previous RIs impossible.

The increase in the Hp concentration after RIT was less pronounced and not significant. A small peak could be seen after 72 h, followed by a slow decrease in concentration without reaching initial values. There was a large variation between different cats, with some showing increased and some decreased concentrations. Overall measurement of the Hp concentration was less helpful to indicate an APR and may not be useful in cats, in general.

The present study shows that RIT might induce a mild APR characterised by an increase in SAA and AGP concentrations that lacks clinical significance in the majority of cases. As all three measured APPs showed both increases and decreases in individual cats, it may be advisable in the future to create an APP profile to prove an APR. According to this study, the combination of SAA and AGP is best suited to monitor APPs after RIT. This is consistent with data in the literature that recommend the combination of a major and a moderate APP.^{14,32}

Conclusions

RIT in hyperthyroid cats induced an APR similar to that seen in humans. It is thus suggestive of systemic, rather than a solely local, inflammatory response after therapy, possibly due to radiation-induced thyroiditis.

AGP and SAA were useful measurands to determine an APR after RIT, although they were not of clinical significance in the majority of cases and not associated with clinical signs in any of the cats.

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Supplementary material The following files are available online:

Analytical performance of APP assays.

Table 1: SAA concentration of 33 cats before (0 h) and 12 h, 36 h, 72 h and 6 days after radioiodine treatment, as well as the x-fold change between different time points (only significant changes) and their maximum increase.

Table 2: AGP concentration of 33 cats 12 h, 36 h, 72 h and 6 days after radioiodine treatment and the x-fold change between different time point (only significant changes).

Table 3: Hp concentrations of 33 cats 12 h, 36 h, 72 h and 6 days after radioiodine treatment.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee, while not specifically required for publication in *JFMS*, was nonetheless obtained, as stated in the manuscript.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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