Journal of Veterinary Behavior 8 (2013) 225–230

Contents lists available at SciVerse ScienceDirect

Journal of Veterinary Behavior

journal homepage: www.journalvetbehavior.com

Research

# The effect of thyroid replacement in dogs with suboptimal thyroid function on owner-directed aggression: A randomized, double-blind, placebo-controlled clinical trial

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ARTICLE INFO

*Article history:*
Received 11 October 2011
Accepted 31 December 2012
Available online 5 February 2013

*Keywords:*
canine
aggression
hypothyroidism
subclinical thyroiditis

ABSTRACT

The efficacy of thyroid hormone replacement therapy (THRT) as treatment for owner-directed aggression in client-owned dogs with borderline low thyroid hormone levels was evaluated by means of a 6-week-long, parallel design, double-blind placebo-controlled study. The designation of "borderline hypothyroid" was made if the dog's free normal thyroxine (T4) value was frankly low or in the bottom 20th percentile of the normal range and either total T4, total triiodothyronine (T3), or free T3 was frankly low or in the bottom 30th percentile of the normal range. The presence of thyroid autoantibodies also qualified a dog for enrollment. Owners recorded the number of aggressive episodes directed toward family members on a daily basis for 8 weeks (2-week baseline phase and 6-week study phase). Twenty-nine dogs completed the study; 14 in a treatment group and 15 in a placebo group. The median number of aggressive episodes per day decreased significantly from baseline in both treated and placebo group dogs in weeks 1-2, 3-4, 5-6, and week 6 (treatment, $\chi^2 = 24.8$, $P < 0.001$; placebo, $\chi^2 = 20.2$, $P < 0.001$), however the median frequency of aggression was significantly lower in the treatment group (1.21 episodes/day) than in the placebo group (1.71 episodes/day) during week 6 of the study ($\chi^2 = 4.047$, $P = 0.044$). Three thyroxine-treated dogs had borderline-low thyroid levels on the final day of the study (day 42). When aggression frequency was compared between the treatment and placebo groups after the removal of 3 thyroxine-treated dogs, the treatment group did not have a significantly lower aggression frequency than the placebo group during week 6 (Kruskal–Wallis statistic: $\chi^2 = 3.035$, n = 26, $P = 0.08$). The authors discuss the role of thyroid hormones in the regulation of aggression and other cognitive issues and provide rationale for using THRT in dogs exhibiting owner-directed aggression that also have low normal or baseline thyroid hormone levels.



## Introduction

It is not surprising that a wide range of behavioral signs and symptoms have been reported in hypothyroid subjects be they human or animal. Even in the early stages of human disease, reduced cognition (Bono et al., 2004) and concentration (Geracioti, 2006) as well as impaired short-term memory (Begin et al., 2008) are reported. Humans may also experience visual and auditory hallucinations, a wide spectrum of fear-based behaviors, mood swings, and aggressive behavior (Denicoff et al., 1990). In hypothyroid dogs, fear-based behaviors (noise and storm phobia, separation anxiety), hyperactivity, poor focus/learning, compulsive behaviors, and aggression (primarily

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http://dx.doi.org/10.1016/j.jveb.2012.12.059

owner-directed or possessive aggression) have been reported (Aronson and Dodds, 2005). Two recent studies, both with relatively small sample size, compared the values of thyroid analytes in dogs with and without behavior problems. In these studies, none of the mean thyroid analytes measured fell outside the normal reference ranges in dogs with or without behavior problems (Carter et al., 2009; Radosta et al., 2011). One retrospective study with a large sample size showed a positive association between aggression and subclinical thyroiditis (defined by elevated thyroglobulin autoantibodies in conjunction with normal thyroxine [T4] and thyroid stimulating hormone [TSH] levels) but not with clinical hypothyroidism (Graham et al., 2003). Clinically, we have also observed a therapeutic effect on anxiety-related and aggressive behavior problems when dogs with borderline or suboptimal thyroid function are treated with a standard dose of thyroxine after 6 weeks or less. Stress often potentiates behavioral issues. Glucocorticoids released in response to stress reduce the pituitary release of TSH in response to thyroid releasing hormone, reduce conversion of T4-T3, and prevent T3 binding to receptors at the cellular level (Re et al., 1976; Cavalieri et al., 1984; Kaptein et al., 1992).

Triiodothyronine (T3) is integral to metabolism throughout the body. In the brain, T4 is converted to T3 and acts directly on neurons. T3 not only can modulate the activity of the neurotransmitters norepinephrine, serotonin, and dopamine and the sensitivity and concentration of their receptors (Bauer et al., 2008) but also can act as a neurotransmitter itself (Dratman and Gordon, 1966). In human psychiatric patients, thyroid hormone supplements are used to augment the effect of antidepressants in refractory euthyroid patients (Cooper-Kazaz et al., 2007) or to accelerate the results of therapy (Altshuler et al., 2001). T3 activity in the brain is affected by many things, including the circulating concentrations of TSH, T3, and T4; availability of unbound hormone; activity of transporters that bind and transport the hormones into cells (Oppenheimer & Schwartz, 1985; Friesema et al., 2006); deiodinase enzymes that convert T4 to the active T3 (Hernandez et al., 2010); and activity of thyroid receptors. The aforementioned last 3 can all be affected by individual genetic variation (Peeters et al., 2006), and it is also true that circulating thyroid levels do not necessarily predict thyroid activity in the brain (Obregon et al., 1984).

So far, documentation of the beneficial effects of treating borderline-low thyroid levels on canine aggression has taken the form of case reports (Dodman et al., 1995; Fatjó et al., 2002). Double-blind placebo-controlled studies are considered the gold standard for determining the efficacy of a particular treatment. In the study reported in the article, we have adopted this approach to evaluate the therapeutic efficacy of thyroxine supplementation for dogs exhibiting owner-directed aggression that also have suboptimal serum thyroid levels.

## Materials and methods

Participants were enrolled in the study between 2005 and 2010. Owners were solicited via Tufts Cummings School of Veterinary Medicine's (TCSVM) Animal Behavior Clinic newsletter Your Dog, magazine adverts, breed-specific chat forums, and a mailing to veterinarians in the New England (United States) area. Local and referring veterinarians aided in the enrollment of participants by submitting samples for a complete blood count, chemistry profile, and a full thyroid panel (performed in the Hemolife Diagnostic Laboratory at Hemopet, California).

### *Enrollment criteria*

#### *Behavioral*

To qualify for the study, dogs had to have resided in the current home for at least 6 months and have shown aggression (growl, lift lip, snap, or bite) in at least 4 of 28 situations (Table 1). Owner-directed aggression, herein defined as any "apparently unprovoked growl, lip lift, snap or bite directed at any human member of the household in which the dog resides," had to occur with a frequency of more than 3 times per week. Owners who indicated that their dog delivered uninhibited bites or had young children in the home were not eligible to participate in the study and were referred to the Animal Behavior Clinic for immediate treatment. Owners had to be willing to refrain

**Table 1**
Percent of dogs that growled, lip lifted, snapped, or bit in response to the following interventions by household members

| Interventions | Remote participants (n = 20), % | In-clinic participants (n = 9), % |
|---|---|---|
| Touch dog's food or add food while eating | 70 | 44 |
| Walk past dog while eating | 25 | 33 |
| Take away real bone, rawhide, or delicious food | 65 | 56 |
| Walk by dog when s/he has a real bone/rawhide | 55 | 44 |
| Touch delicious food when dog is eating | 45 | 56 |
| Take away a stolen object | 70 | 44 |
| Physically wake dog up or disturb resting dog | 75 | 89 |
| Restrain dog when it wants to go someplace | 55 | 22 |
| Lift dog | 65 | 33 |
| Pet dog | 40 | 33 |
| Medicate dog | 45 | 11 |
| Handle dog's face/mouth | 35 | 22 |
| Handle dog's feet | 65 | 22 |
| Trim the dog's toenails | 70 | 44 |
| Groom dog | 60 | 44 |
| Bathe or towel off | 45 | 11 |
| Take off or put on collar | 20 | 11 |
| Pull dog back by the collar or scruff | 60 | 33 |
| Reach for or grab dog by the collar | 55 | 33 |
| Hold dog by the muzzle | 40 | 44 |
| Stare at the dog | 35 | 33 |
| Reprimand dog in loud voice | 40 | 56 |
| Visually threaten dog: newspaper or hand | 30 | 0 |
| Hit the dog | 45 | 11 |
| Walk by dog in crate | 10 | 11 |
| Walk by/talk to dog on furniture | 45 | 56 |
| Remove dog from furniture: physically or verbally | 85 | 44 |
| Make dog respond to command | 45 | 22 |

from trying any new treatments for the dog's aggression for the duration of the study. Owners of dogs that were currently being treated with psychotropic medication were required to discontinue the medication (under the discretion of the prescribing veterinarian) for at least 2 weeks before having their dogs' thyroid levels tested. Only one dog was being treated with psychotropic medication (fluoxetine) and had it withdrawn to enroll in the study. The dog had been on fluoxetine for 1.5 years, and the owners did not regard it as usefully therapeutic. One other dog was being treated with a subeffective dose of 5-hydroxytrypophan (5HTP) for an unknown duration before enrollment. The 5HTP was discontinued 2 weeks before the study.

*Thyroid level requirement*

Dogs had to be showing at least one of the following clinical signs of hypothyroidism to qualify for free thyroid panel testing: excessive shedding, patchy hair loss or "rat tail," dry skin or dull, dry hair coat, recurrent infections, tendency to gain weight, heat-seeking behavior, increased sleep time, hyperactivity, slow learning, seizures, worried look, tragic facial expression or looking "old," reduced hearing, sight and/or scenting ability, chronic gastrointestinal signs, loss of muscle or bladder tone, head tilt, change in character of bark, exercise intolerance, infertility, false pregnancy or weak, dying, or stillborn puppies, and/or recurring eye infections. To qualify for the study, a dog's free T4 level had to be frankly low or in the bottom 20th percentile of the normal range and either the total T4, total T3, or free T3 had to be frankly low or in the bottom 30th percentile of the normal range. The presence of thyroid autoantibodies also qualified a dog for enrollment. Ninety-eight dogs met the behavioral enrollment criteria and had full thyroid panels performed. Forty dogs met all the behavioral and thyroid requirements. One of the 40 dogs had frankly low total and free T3 and T4 levels and an elevated level of thyroglobulin autoantibody (autoimmune thyroiditis).

*Experimental protocol*

This study used a double-blind placebo-controlled parallel design. The study protocol was reviewed and accepted by TCSVM's Clinical Research Studies Committee. The owners of qualifying dogs signed a consent form and were given a data collection form to aid in the completion of a 2-week long baseline phase (BP) during which time they recorded the number of growls, lip lifts, snaps, or bites delivered to household members each day. The mean number of aggressive episodes (i.e., growls, lip lifts, snaps, or bites) per day over the 2-week long BP comprised our baseline aggression score. Owners were then randomly and blindly assigned to either a thyroxine treatment group or a placebo group via TCSVM's pharmacy department personnel. Both the placebo and thyroxine (Soloxine) tablets were donated by Virbac Corporation. The placebo pills were color coded according to their purported milligram size and matched the appearance of the color-coded thyroxine tablets. Dogs were dosed according to their weight using the dose range of 0.1 mg per 10-15 pounds body weight (4.5-6.8 kg). Owners were instructed to give this dose twice daily. An 8-week supply of medication was given directly to local participants or mailed to remote clients' local veterinarians for distribution. Owners were given a second data collection form in which to record the number of growls, lip lifts, snaps, or bites delivered to household members every day for 6 consecutive weeks. The mean number of aggressive episodes directed to household members per day during weeks 1 and 2, weeks 3 and 4, weeks 5 and 6, and week 6 composed our aggression frequency scores and basis for comparison. Owners were contacted every other week to monitor compliance. On the last day of the 6-week trial, owners returned to TCSVM's Animal Behavior Clinic or to their local veterinarian's office to be unblinded. A full thyroid panel was performed for thyroxine-treated dogs, 4-6 hours after dose was given. Owners of untreated dogs were given the opportunity to try thyroxine treatment. Owners who reported no clinical benefit from thyroid supplementation were advised to wean their dogs off thyroid supplementation. Behavior modification and management advice were also provided to all owners at this time.

*Statistical analysis*

Signalment and participant type (TCSVM clinic vs. remote) were analyzed via Fisher exact tests. Age of dog was normally distributed, and a *t* test was used to detect a difference. The number of aggressive episodes (growling, lip lifts, snaps, and bites) per day during the BP was not normally distributed, and nonparametric statistics were used. Friedman test (repeated measures) was used to detect a difference in the median number of aggressive episodes per day between the baseline period, weeks 1-2, weeks 3-4, weeks 5-6, and week 6 in both the placebo and treatment groups. A series of Wilcoxon signed rank tests (repeated measures) were used to detect differences within each group in the median number of aggressive episodes per day for weeks 1-2, weeks 3-4, weeks 5-6, and week 6. A Kruskal–Wallis test was used to compare the median number of aggressive episodes per day between the placebo and treatment groups during weeks 1-2, weeks 3-4, weeks 5-6, and week 6. Statistical significance for the outcome was measured at the 95% level ($P < 0.05$).

## Results

*Subjects*

Twenty-nine of the 40 dogs that met the behavioral and thyroidal inclusion criteria completed the study (14 dogs in the treatment group and 15 dogs in the placebo group). Eleven dogs did not complete the study. Three owners misplaced their data forms, one owner fell ill, 3 dogs were dropped from the study because of the owner's concern about the lack of improvement in aggression (2 of these dogs were being treated with placebo), 3 owners dropped out while waiting for the thyroxine and placebo pills to get shipped out, and one we withdrew because a family member moved out of the home, which dramatically reduced the number of aggressive episodes.

**Table 2**
Signalment of group (n = 29)

| Characteristics | Treatment (n = 14) | Placebo (n = 15) | *P* |
|---|---|---|---|
| Age (y), mean (SD), *df* = 27 [range] | 4.6 (2.1) [1-9] | 6.2 (3.3) [1-12] | 0.14 |
| Sex, N (% female) | 3 (21) | 5 (33) | 0.68 |
| Breed, N (%) | | | |
| Toy | 0 | 4 (27) | 0.11 |
| Sporting | 4 (29) | 2 (13) | |
| Nonsporting | 1 (7) | 0 | |
| Herding | 0 | 3 (20) | |
| Working | 3 (21) | 1 (7) | |
| Hound | 1 (7) | 0 | |
| Terrier | 5 (36) | 4 (27) | |
| Mix | 0 | 1 (7) | |
| Weight >20 lb, N (%), [range] | 12 (86) [5-140] | 8 (53) [6-105] | 0.07 |
| Neutered, N (%) | 12 (86) | 13 (87) | 1.00 |
| TCSVM participants, N (%) | 1 (7) | 8 (53) | 0.014 |
| BP # of aggressive episodes/day mean (SD) [range] | 3.9 (1.9) [2-9] | 5.5 (3.9) [1-13] | 0.34 |

SD, standard deviation; TCSVM, Tufts Cummings School of Veterinary Medicine; BP, baseline phase.

Signalment and our clinic versus remote participant status by group are presented in Table 2. There were significantly more remote participants in the treatment group versus the placebo group. In all other respects, the 2 groups did not differ significantly. The mean number of owner-reported attributable signs of hypothyroidism per dog was 4.5 (standard deviation = 2.7).

## *Aggression*

### *Within-group comparisons*

In both the treatment and placebo groups, Friedman test showed a significant difference in the aggression scores associated with the baseline period, weeks 1-2, 3-4, 5-6, and 6 (treatment group, $\chi^2 = 24.8$, n = 4, $P < 0.001$; placebo group, $\chi^2 = 20.2$, n = 4, $P < 0.001$). For both groups, the aggression score decreased significantly from baseline at weeks 1-2, 3-4, 5-6, and 6 (Table 3). The sixth week of treatment was examined exclusively because, from our clinical experience, it is an important time frame in terms of owners reporting a behavioral response.

### *Between-group comparisons*

When the baseline and treatment phase aggression frequency scores were compared between the treatment and placebo groups, the treatment group had a significantly lower aggression frequency during week 6 than the placebo group did during week 6 (Kruskal–Wallis statistic: $\chi^2 = 4.047$, n = 29, $P = 0.04$) (Table 4). The median aggression frequency for the treatment group during week 6 was 1.21 episodes/day, whereas for the placebo group it was 1.71 episodes/day. Three dogs were excluded because their thyroid levels remained borderline low when rechecked on day 42. When the aggression scores were again compared between the treatment and placebo groups, the treatment group did not have a significantly lower aggression score than the placebo group during week 6 (Kruskal–Wallis statistic: $\chi^2 = 3.035$, n = 26, $P = 0.08$).

## *Thyroid levels*

Hemopet's reference ranges for total T4 and free T4 thyroid values changed several times during the course of the trial (Table 5), primarily because the manufacturers no longer supplied the assay reagents or more accurate and precise methodology replaced the former methods. The mean total T4 and free T4 values for both the treatment and placebo groups were borderline low and fell just below the lower end of the normal range or were within the lowest 20th percentile. After treatment, the total T4 and free T4

**Table 3**
Differences in MASs within the placebo and treatment groups

| Group | Phase | Mean (SD) | MAS (range) | Z | *df* | *P* |
|---|---|---|---|---|---|---|
| Treatment | Baseline | 3.76 (2.0) | 3.04 (6.8) | NA | NA | NA |
| (n = 14) | Weeks 1-2 | 2.84 (2.6) | 2.04 (10.5) | −2.237 | 13 | 0.025* |
| | Weeks 3-4 | 1.98 (1.7) | 2.00 (6.7) | −3.059 | 12 | 0.002* |
| | Weeks 5-6 | 1.87 (1.6) | 1.39 (6.4) | −3.040 | 13 | 0.002* |
| | Week 6 | 1.42 (0.99) | 1.21 (3.4) | −3.045 | 14 | 0.002* |
| 0.5 | | | | | | |
| Placebo | Baseline | 5.50 (3.9) | 5.87 (12.8) | NA | 15 | NA |
| (n = 15) | Weeks 1-2 | 3.84 (2.9) | 3.07 (8.9) | −3.011 | 15 | 0.003† |
| | Weeks 3-4 | 3.32 (2.6) | 3.21 (7.6) | −3.294 | 15 | 0.001† |
| | Weeks 5-6 | 3.20 (2.5) | 2.31 (7.6) | −2.556 | 15 | 0.011† |
| | Week 6 | 3.30 (2.8) | 1.71 (7.7) | −2.329 | 15 | 0.02† |

MASs, median aggression scores; SD, standard deviation; NA, not applicable.
* Indicates a statistically significant difference from treatment baseline at $P < 0.05$.
† Indicates a statistically significant difference from placebo baseline at $P < 0.05$.

**Table 4**
Differences in median aggression scores between the placebo and treatment groups

| Treatment vs. placebo | n = 29 | | | n = 26 | | |
|---|---|---|---|---|---|---|
| | *df* | $\chi^2$ | *P* | *df* | $\chi^2$ | *P* |
| Baseline | 1 | 0.922 | 0.337 | 1 | 0.567 | 0.452 |
| Weeks 1-2 | 1 | 0.488 | 0.485 | 1 | 0.055 | 0.815 |
| Weeks 3-4 | 1 | 1.288 | 0.256 | 1 | 1.132 | 0.287 |
| Weeks 5-6 | 1 | 1.239 | 0.266 | 1 | 0.733 | 0.392 |
| Week 6 | 1 | 4.047 | 0.044 | 1 | 3.035 | 0.081 |

levels increased to just above upper normal or in the higher end of the normal range in most dogs. The total T4 and/or free T4 for 3 of the treatment dogs did not increase into the upper part of the reference range when these levels were rechecked on day 42. The owners of these dogs were asked if, on the day the thyroid levels were rechecked, they had given their dogs the study medication that morning and all 3 owners confirmed that the medication had been administered. These 3 dogs were removed from the analysis, and the statistical analysis of the between-group and within-group aggression scores was repeated.

## Discussion

Owners of 11 dogs who received thyroxine treatment reported significantly fewer incidences of owner-directed aggression during week 6 of the trial than the 15 owners of dogs who gave placebo (n = 26). Importantly, none of the 29 owners reported observing side effects in their dogs as a result of thyroxine treatment during this trial. In terms of deciding clinical treatment for dogs showing owner-directed aggression, the benefit of a possible reduction in aggression frequency may outweigh the risk of any detrimental effects that could occur from a 6-week long trial with thyroxine treatment in dogs showing borderline-low thyroid levels.

Recruiting dogs for the study proved more difficult than anticipated, and in fact, it took us 5 years to accumulate 40 enrollable subjects. Owners of aggressive dogs rarely want to wait even 2 weeks let alone 8 weeks to begin effective treatment for a potentially dangerous problem. As a result, we had to include remote subjects that were not behaviorally evaluated in person and thus their diagnosis might be less certain. It should be noted that more dogs in the treatment group were evaluated elsewhere. Once dogs entered the study, attrition rates were high with more than 25% of the subjects dropping out or having to be excluded. As a result, the number of dogs in each group was small.

For 3 dogs in the treatment group, post-trial thyroid panels did not reveal a substantial increase in thyroid levels and so these dogs were removed from the analysis. Removing them from the analysis caused our already small sample size to become even smaller and increased the variability in the data. This may explain why a significant difference between the 2 groups was not seen after these 3 dogs were removed. One could argue that removing these 3 dogs from the analysis was not necessary. Assessment of thyroid function is still somewhat controversial. Serum thyroid levels fluctuate with the needs of the body, levels of other hormones, nonthyroidal illness, activity level, and giving thyroxine with foods containing calcium or soy, which bind and impair absorption of the drug. These factors might explain why these 3 dogs' thyroid levels did not increase in response to thyroxine treatment. Serum thyroid levels do not always reflect intracellular levels within the central nervous system.

The potential placebo effect noted in this study is observed in many blind and double-blind studies in which owners are advised of what they might expect to see if their dog is in the active treatment group (Dodman et al., 2004; Cottam and Dodman, 2009). This powerful effect clouds the data acquired and decreases the power of the analysis. Even potential side effects attributable to the treatment will be reported by owners of animals in the placebo group (Dodman et al., 1996). This powerful owner-generated placebo effect requires that sufficient numbers of animals be enrolled in any study for a significant difference to be

**Table 5**
Pretreatment and post-treatment total T4 and free T4 values (n = 29)

| | Placebo (n = 15) | | | Treatment (n = 14) | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | n | Reference range | Mean (SD) | n | Reference range |
| Pre T4 | 1.5 (0.6) | 13 | 1-4 μg/dL | 1.4 (0.5) | 11 | 1-4 μg/dL |
| | 0.7 (0.3) | 2 | 0.8-3.8 μg/dL | 0.8 (0.1) | 3 | 0.8-3.8 μg/dL |
| 0.5 | | | | | | |
| Pre free T4 | 0.8 (0.2) | 6 | 0.65-3 ng/dL | 1.0 (0.2) | 6 | 0.65-3.0 ng/dL |
| | 0.5 (0.1) | 7 | 0.45-2.06 ng/dL | 0.5 (0.2) | 5 | 0.45-2.06 ng/dL |
| | 0.4 | 1 | 0.6-2.5 ng/dL | 0.72 | 1 | 0.6-2.5 ng/dL |
| | 0.7 | 1 | 0.55-2.32 ng/dL | 0.7 (0.01) | 2 | 0.55-2.32 ng/dL |
| 0.5 | | | | | | |
| Post T4* | NA | | | 5.1 (1.7) | 11 | 1-4 μg/dL |
| | | | | 2.1 (0.3) | 2 | 0.8-3.8 μg/dL |
| 0.5 | | | | | | |
| Post free T4† | NA | | | 2.4 (1.3) | 3 | 0.65-3.0 ng/dL |
| | | | | 1.1 (0.6) | 7 | 0.45-2.06 ng/dL |
| | | | | 1.48 | 1 | 0.6-2.5 ng/dL |
| | | | | 1.51 | 1 | 0.55-2.32 ng/dL |

SD, standard deviation; NA, not applicable.
* Post T4 level was unavailable for 1 dog.
† Post free T4 level was unavailable for 2 dogs.

measured. Approximately 30%-40% of participants will report a therapeutic effect when given a placebo (Beecher, 1955).

This study required that an accurate measurement of aggression be performed by a lay observer—the owner. For ease of analysis of the results, applying a numerical score to aggression is optimal, yet within the broad categories of growl, snap, and bite there is a vast spectrum of behaviors. For example, there are dogs that growl in much the same way as cats purr. Subjectively, this is not an aggressive act, but objectively a growl is a growl. It is possible that our method for measuring the frequency of owner-directed aggression was suboptimal. Preferably, a validated tool for measuring the frequency of owner-directed aggression in client-owned dogs would have been used, however, to our knowledge, no such validated tool exists. It is possible that owners' investment in the study diminished overtime, and they did not always remember to record aggressive episodes or that other family members failed to report all incidents. This could be one explanation for the decrease in aggressive episodes over time in both groups. The amount of time that the dogs were left home alone and the home environment of the dogs in this study could have affected the frequency of aggression recorded for any particular dog.

The dogs included in this study may not reflect the population of dogs at large or those that present for aggression to a veterinary behaviorist. This is because the most aggressive dogs were of necessity treated immediately; delaying treatment for the study period if the dogs were randomly placed in the placebo group would be unethical, particularly in a household with children present. If dogs with higher frequencies of aggression than those that were enrolled in this study had been included, it may be that a more substantial reduction in the frequency of aggression would have been seen. Additionally, if we had lengthened the trial's duration to 8 weeks or had limited the hormonal diagnostic criterion to be the 10th percentile of the normal range, we may have seen more marked individual responses and had a more robust end result.

The results of this study show only a weak and somewhat equivocal effect of thyroid hormone replacement therapy (THRT) in dogs with borderline thyroid hormone levels and owner-directed aggression. As such, THRT cannot be wholeheartedly endorsed at this time for treatment of aggressive dogs with borderline-low thyroid status, as we defined it. Further studies are warranted into the putative association of low thyroid status and canine owner-directed (also known as conflict) aggression and thus the potential benefit of boosting thyroid hormone levels as a therapeutic measure in such cases.

## Acknowledgment

The authors thank the Virbac Corporation for donating Soloxine and color-coded placebo pills for use in the study.

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