Evaluation of Fortetropin in geriatric and senior dogs with reduced mobility

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Abstract — As pets age, quality of life and mobility can be affected by pain of osteoarthritis and age-related muscle atrophy (sarcopenia). The purpose of this randomized, double-blinded, placebo-controlled study was to evaluate the effects of Fortetropin, a nonthermal-pasteurized, freeze-dried, fertilized egg yolk product, on mobility in senior dogs. Mobility scores were calculated using a standardized and validated client-based survey: the Liverpool Osteoarthritis in Dogs (LOAD) questionnaire. Results showed mild, but statistically significant, improvement of the mobility scores for the treatment group at both week 6 ($P = 0.03$) and week 12 ($P = 0.006$) compared to the baseline score. No statistical improvement was noted at any time in the placebo group or between the treatment and placebo group.

Résumé — Évaluation de Fortetropin chez les chiens gériatriques et âgés à mobilité réduite. À mesure que les animaux de compagnie vieillissent, la qualité de vie et la mobilité peuvent être touchées par la douleur causée par l'arthrose et l'atrophie musculaire liée à l'âge (sarcopénie). Le but de cette étude randomisée, à double insu et contrôlée par placebo était d'évaluer les effets de Fortetropin, un produit non pasteurisé, lyophilisé et fertilisé de jaune d'œuf, sur la mobilité chez les chiens âgés. Les cotes de mobilité ont été calculées à l'aide d'un sondage standardisé et validé mené auprès des clients, le questionnaire *Liverpool Osteoarthritis in Dogs* (LOAD). Les résultats ont montré des scores statistiquement améliorés de mobilité pour le groupe de traitement à la semaine 6 ($P = 0{,}03$) et à la semaine 12 ($P = 0{,}006$) comparés au score de ligne de base. Aucune amélioration statistique n'a été notée à n'importe quel moment dans le groupe de placebo ou entre le groupe de traitement et de placebo.

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The aging of pet dogs is rapid compared with that of humans and presents health challenges that can affect quality of life (1,2). Even in the absence of life-threatening diseases (*e.g.,* cancer, chronic kidney disease), quality of life can be affected by chronic pain [such as osteoarthritis (OA) and age-related muscle atrophy (sarcopenia)] that can limit mobility. The dog's ability to rise without assistance, go for walks, or move through the house to be with the family can all be affected by reduced mobility. Consequently, pet owners may develop a pessimistic perception of their dog's quality of life.

Osteoarthritis was estimated to have an annual period prevalence of 2.5% in a study of almost 500 000 dogs in the United Kingdom (3). In that study, the greatest odds ratio for OA was associated with older age and OA was estimated to affect 11.4% of affected dogs' lifespan (3). The administration of analgesics, especially non-steroidal anti-inflammatory drugs, is the most often employed treatment for OA but does not address sarcopenia (3). The addition of a daily joint supplement has also been shown to improve clinical signs associated with osteoarthritis (4). Physical rehabilitation, such as swimming and using an underwater treadmill, have been shown to be effective strategies to improve mobility and reduce pain in dogs with OA by improving muscle mass and strength (5). For dog owners who lack accessibility to physical rehabilitation centers, alternative strategies to minimize sarcopenia are needed.

Sarcopenia, which has been documented in older Labrador retrievers (> 8 y of age) in the absence of an increase in inflammatory mediators, appears to predict early mortality. The maintenance of lean body mass was shown to be important for longer lifespans in Labrador retrievers (6). In 1 study, sarcopenia and other forms of muscle atrophy were shown to be directly linked to increased expression of myostatin, an inhibitor of muscle growth and promoter of muscle atrophy, even though the initiators of myostatin expression were not defined (7). Inhibition of myostatin has been shown to reverse or prevent muscle atrophy in various rodent models of disease states, including disuse atrophy; but was of no benefit in dogs with cardiac cachexia (8,9).

Fortetropin (Canine Muscle Formula; Myos, Cedar Knolls, New Jersey, USA), a nonthermal-pasteurized, freeze-dried, fertilized egg yolk product, was shown to have an abundance of pro-angiogenic and host-defense proteins compared to unfertilized

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egg yolk (10). Fortetropin is believed to promote muscle growth through the reduction of serum myostatin through an undefined mechanism, yet the measured effect on serum myostatin levels has varied in studies (11,12). Fortetropin reduced serum myostatin levels and altered downstream signaling pathways consistent with myostatin inhibition in humans and rats in one study and prevented a rise in serum myostatin, compared with a placebo, when given to dogs during an 8-week period of forced exercise restriction following tibial plateau leveling osteotomy in another study (11,13). However, a study in older men and women demonstrated no change in serum myostatin over 21 d of Fortetropin administration, despite demonstrating an 18% increase in the fractional synthetic rate of muscle protein in comparison to a placebo (13).

The Liverpool Osteoarthritis in Dogs (LOAD) questionnaire is a client-based clinical metrology instrument that has been validated for use in dogs with osteoarthritis and uses owner-friendly terminology to create a numerical score associated with mobility (14). LOAD has been demonstrated to correlate with force-platform data thus linking the LOAD mobility scores to objective data (14). LOAD mobility scores range from 0 (normal mobility) to 52 (severe mobility problems). Although not all affected dogs had a diagnosis of osteoarthritis confirmed by radiographs, all had clinical signs associated with osteoarthritis. Based on their clinical signs, the LOAD questionnaire was used as an objective measurement of mobility in this study.

The purpose of this study was to evaluate the effects of Fortetropin on mobility in a double-blinded, placebo-controlled fashion over a 12-week period using the LOAD questionnaire. Institutional Animal Care and Use Committee approval was obtained for this study. Dogs were included in the study if they had a stable appetite, unchanged drinking and urination habits, an alert mental status, and were affected by at least 3 of the following in the opinion of the pet owner: lameness, weakness, decreased mobility (*e.g.,* difficulty jumping or doing stairs), decreased voluntary activity, subjective loss of muscle mass, or reduced exercise tolerance. Dogs needed to meet the minimum age requirements for senior dogs (Table 1) (15). Dogs were excluded from the study if they were known to have any disease that would negatively affect survival of at least 6 mo (*e.g.,* cancer affecting any internal organ, chronic kidney disease of IRIS Stage 3 or greater, Stage C or D endocardiosis, degenerative myelopathy). If a complete blood (cell) count, serum biochemistry profile, and urinalysis were not performed within the previous 3 mo and available for review, they were performed before inclusion. Dogs were not excluded from the study if they were receiving medications for epilepsy, osteoarthritis, atopy, diabetes mellitus, or others deemed necessary that would not impact the study (*e.g.,* cyclosporine ophthalmic, heartworm, and flea preventatives). Dogs were not excluded for age-related changes that would not immediately affect their survival.

Forty-six dogs were enrolled in the study to completion. Physical examination was performed at the Kansas State University Veterinary Health Center (KSUVHC) and health status confirmed at weeks 0 and 12 by the same investigator (MCH) for 24 dogs. Restrictions enforced during the COVID-19 pandemic prevented Week 12 examination in 12 dogs and no in-person evaluation of 10 dogs. Owners signed an informed consent waiver and then were asked to complete the Liverpool Osteoarthritis Dog (LOAD) mobility questionnaire at baseline (Week 0) and at the end of Weeks 6 and 12 of the study. Modifications to language in the LOAD mobility questionnaire were made as necessary for an American audience. Dogs were randomized based on size (small, medium, large, giant) to receive 1 of 2 macronutrient-matched products, which were provided in white plastic canisters. Product "A" was Fortetropin (33% protein, 55% fat, 7% carbohydrate) and product "B" was a cheese powder (36% protein, 48% fat, 4% carbohydrate), each provided by Myos Corp. Clients and investigators were blinded to the treatment and placebo agent. The powder was administered with the dog's meal and mixed with the food. Dogs were dosed based on manufacturer recommendations as follows: dogs up to 11.4 kg received one scoop (3 g) daily; dogs 11.4 to 22.7 kg received 2 scoops (6 g) daily; dogs $>$ 22.7 kg received 4 scoops (12 g) daily (an included scoop measured 3 g). At the end of the 12-week supplement feeding period, owners were asked to bring dogs for a final physical examination.

Statistical evaluation was performed (JKR) with blinding both to the control and treatment groups and scoring interpretation. Age and weight were compared with an independent *t*-test. Comparison of LOAD mobility scores between the 2 groups from Weeks 0, 6, and 12 and the change in scores between Weeks (0–6, 0–12, and 6–12) were compared with a non-parametric *t*-test (Mann-Whitney *U*-test). Within each group, LOAD mobility scores were compared for each time period (0 *versus* 6, 0 *versus* 12, and 6 *versus* 12) with Friedman's test for repeated measures over time. Significance was set at $P < 0.05$. Statistical analysis was performed with commercial software (WINKS 7.0.9 Professional Edition, TexaSoft; WINKS SDA Software, Cedar Hill, Texas, USA).

There were 23 dogs each in the treatment (A) and placebo (B) groups. The distribution of dogs by size was similar between groups (Table 1). There was no significant difference in age, weight, or LOAD mobility scores at Weeks 0, 6, or 12 between the 2 groups (Table 2). There was a statistically significant difference in LOAD mobility scores between Weeks 0 and 6 and Weeks 0 and 12 in the treatment group but not in the placebo group (Table 2), even though there was no statistically significant difference between the groups at any time point. The control group had a larger range and interquartile range in LOAD scores for all 3 time points compared with the treatment group (Table 2). The resulting large variance in the control group compared with the treatment group likely is the reason for a statistical difference within groups but not between groups. Therefore, this statistically significant difference within the treatment group may not reflect a clinically relevant change. In addition, the failure to detect a statistical difference in LOAD mobility scores between the placebo and treatment groups could reflect a lack of power to recognize a difference between the 2 groups. With similar results, a future study would need 50 dogs in each group to identify a statistical difference at each time point.

An additional factor that could have affected the statistical interpretation was the reliance on the dog owners' ability to

Table 1. Distribution of dogs in each treatment group for different senior weight and size classifications and clinical signs reported by owners for each treatment group.

	Weight groups with minimum age for senior designation [number of dogs in each group (median age in years; range)]				Clinical signs reported by owners (number of dogs in each group)				
Group	< 9.1 kg (small; 9 y)	9.1 to 22.9 kg (medium; 7 y)	23.0 to 54.5 kg (large; 6 y)	> 54.5 kg (giant; 4 y)	Lameness	Decreased mobility and/or weakness	Exercise intolerance	Decreased voluntary activity	Muscle mass loss
Fortetropin	5 (12 y; 9 to 13.1 y)	6 (12.6 y; 9 to 14.1 y)	11 (10.8 y; 8 to 12 y)	1 (7.4 y)	13	20	12	12	17
Cheese powder	3 (11.8 y; 11.1 to 14 y)	4 (11.9 y; 8 to 12 y)	15 (9.9 y; 7 to 13 y)	1 (9.7 y)	12	20	7	11	17

Table 2. Age, weight, LOAD mobility scores, statistical comparison of scores and number in each group with lower, unchanged, or higher scores at Week 12 compared to Week zero for dogs receiving Fortetropin or cheese powder.

	Fortetropin	Cheese powder	*P*-value
Age (y)	11.5 (7.4 to 14.1); 10.9 (1.8) (*n* = 23)	11 (7.1 to 14); 10.6 (2.3) (*n* = 23)	0.58
Weight (kg)	24.4 (2.5 to 63.3); 23.4 (14.9) (*n* = 23)	25 (3.3 to 59.8); 23.7 (12.7) (*n* = 23)	0.59
LOAD score, Week 0	21 (10 to 31, 18 to 26); 21.35 (5.7, 30.9) (*n* = 23)	22.5 (12 to 45, 18 to 30); 23.71(7.9, 62.7) (*n* = 23)	0.425
LOAD score, Week 6	19 (9 to 29, 17 to 24); 19.67 (4.9, 20.5) (*n* = 21)	22 (7 to 43, 16 to 29); 23.69 (9.7, 80.7) (*n* = 21)	0.521
LOAD score, Week 12	19 (9 to 31, 17 to 23); 19.05 (5.1, 23.9) (*n* = 22)	17 (10 to 45, 15 to 28); 21.04 (9.1, 86.1) (*n* = 23)	0.972
Week 0 *versus* 6	*P* = 0.0352[a] (*n* = 21)	*P* = 0.1612 (*n* = 21)	0.687
Week 0 *versus* 12	*P* = 0.0065[a] (*n* = 22)	*P* = 0.1359 (*n* = 23)	0.785
Week 6 *versus* 12	*P* = 0.2219 (*n* = 20)	*P* = 0.3129 (*n* = 20)	0.967
Weeks 0, 6, 12	*P* = 0.036[a] (*n* = 20)	*P* = 0.106 (*n* = 20)	
Lower LOAD score [number (%) (median change)]	14 (61%) (−3)	12 (52%) (−8)	
Unchanged LOAD score [number (%)]	5 (22%)	4 (17%)	
Higher LOAD score [number (%) (median change)]	4 (17%) (+2)	7 (30%) (+5)	

Values are reported as [(median, range) mean (± SD) (number of dogs)] for age, weight, and LOAD score (interquartile range and variance is also listed [(median, range, interquartile range) mean (± SD, variance) for LOAD scores]. Number of complete data sets shown for comparisons of weeks. Intergroup comparison (*P*-value) shown in right-hand column. Intragroup comparison (*P*-value) shown in same column with treatment group. Statistically significant difference noted by *.
[a] Statistically significant difference.

objectively complete the LOAD survey with no bias or momentary influence (*e.g.,* activity affected by extremes of weather or variable personal circumstances). In the absence of quantifiable objective data, it must be considered that owners' interpretation of the questions and their answers could be altered with time (*i.e.,* a similar level of activity could result in a different score). It was hoped that an examination of each dog could be performed by the same investigator (MCH) at Weeks 0 and 12; however, as stated above, this was possible for only 24 dogs (16 dogs from the treatment group and 8 dogs from the placebo group). Although the investigators were also blinded, subjectively there was an appreciable difference in dogs that were in the treatment group (8 dogs had improved muscle mass and mobility; 8 dogs were considered to have stable muscle mass and mobility; and no dogs were considered worse) compared with the placebo group [1 dog had improved muscling and mobility, whereas 4 (50%) were stable and 3 (38%) had lost muscle mass and had reduced mobility]. However, given that the dogs were seen only twice, these assessments also lack quantifiable objective measurements. Including a purely quantifiable outcome through activity monitors was initially attempted in 16 dogs, but owners found these monitors difficult to use and the data were frequently incompatible with reported observed activity.

All participants were questioned on the ease of administering the powders and any refusal by their pet. Both powders were considered easy to administer by all but one individual (treatment group). Within the treatment group one dog was noted to be averse to the product, whereas 3 dogs within the placebo group refused the powder. Fortetropin was enthusiastically ingested by most dogs and was widely considered easy to administer by their owners.

The use of medications to treat OA was not an exclusion criterion in this study, and it was considered unethical for these medications to be stopped in dogs that required them

for pain relief. During the study, no dog on medication associated with pain relief from OA had a change in dose, type, or frequency of medication. In addition, no dog started any new medication during the study period. In the treatment group, 10 of 23 patients were receiving medication to control pain associated with joint disease [grapiprant (n = 3 dogs), carprofen (n = 3 dogs), meloxicam alone (n = 1), tramadol alone (n = 2), and tramadol with meloxicam (n = 1)], whereas 7 of 23 dogs in the placebo group were on similar medication [carprofen (n = 3 dogs), grapiprant (n = 2), aspirin (n = 1), and prednisone (n = 1)].

Lastly, in the 10 dogs that did not have an in-person examination, it is difficult to be certain that no other underlying systemic diseases were contributing to a decline in mobility. Although it is possible this could have occurred, this group of 10 dogs was included as they were owned by veterinarians or had a close relationship with a veterinarian (*e.g.,* employee, co-worker, friend).

This study showed a mild and variable improvement in mobility in geriatric and senior dogs with the administration of Fortetropin as determined by the LOAD mobility scores. Further studies will need to reveal the clinical relevance of the findings of this study and which dogs will benefit most from Fortetropin supplementation.

Fortetropin supplementation may offer an at-home alternative or additional treatment option to out-patient physical therapy for improving mobility and may augment, or even reduce the need for, analgesic and anti-inflammatory therapy in dogs with reduced mobility due to osteoarthritis. CVJ

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