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ORIGINAL ARTICLE

Effects of feeding a high omega-3 fatty acids diet in dogs with naturally occurring osteoarthritis

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Summary

The aim of this randomized, placebo-controlled and double-blinded trial was to compare the effect of a veterinary therapeutic diet (VTD) rich in omega-3 fatty acids (omega-3) from fish origin to a regular diet used as control (CTR) over a period of 13 weeks in dogs afflicted by naturally occurring osteoarthritis (OA). Thirty privately owned dogs were selected. Dogs had lameness confirmed by an orthopaedic examination, had stifle/hip OA and had locomotor disability based on the peak of the vertically oriented ground reaction force (PVF) measured using a force platform. At Baseline, all owners were asked to determine 2–5 activities of daily living that were the most impaired. Activities were scores (0–4) in accordance with severity using case-specific outcome measures (CSOM). The PVF was also measured. Dogs (15/group) were then randomly assigned to receive either the CTR or the VTD. The CSOM was completed twice weekly. The recording of PVF was repeated at Week 7 and 13. The VTD-fed dogs showed a significantly higher PVF at Week 7 ($p < 0.001$) and at Week 13 ($p < 0.001$) when compared to Baseline. From Baseline to Week 13, VTD-fed dogs had a mean (± SD) change in PVF recording of 3.5 ± 6.8% of body weight (%BW) compared with 0.5 ± 6.1%BW ($p = 0.211$) in CTR-fed dogs. This change in primary outcome was consistent with an effect size of 0.5. Conversely, dogs fed the CTR did not show significant change in PVF measurements. At the end of the study, the CSOM was significantly decreased ($p = 0.047$) only in VTD fed dogs. In lame OA dogs, a VTD that contains high level of omega-3 from fish origin improved the locomotor disability and the performance in activities of daily living. Such nutritional approach appears interesting for the management of OA.

Introduction

Canine osteoarthritis (OA) is one of the most common orthopaedic disorders in dogs (Johnston, 1997). Systematic reviews of the therapeutic management of canine OA have been recently published, addressing the innovative use of veterinary therapeutic diet (VTD) in afflicted dogs (Aragon et al., 2007; Sanderson et al., 2009). Such nutritional approaches are appealing to dog owners, as they provide substances claimed to possess beneficial properties beyond supplying the daily nutrient needs. Among these supplemented substances are long-chain polyunsaturated omega-3 fatty acids (omega-3), which are

highly concentrated in flaxseed, fish and their derivatives (Folador et al., 2006; Bauer, 2007; Biondo et al., 2008). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are among the omega-3 recognized to provide benefits against an array of disorders and conditions in canines (Miller et al., 1992; Brown et al., 2000; Bauer, 2007; Biondo et al., 2008; Hansen et al., 2008; Laurent et al., 2008; LeBlanc et al., 2008; Kirby et al., 2009).

For veterinarians having to manage dogs afflicted by OA, optimal decision-making may be compromised by the absence of randomized, controlled and double-blinded clinical trials for every specific VTD available. As it was the case for several cyclooxygenase-2-specific inhibitors (Aragon et al., 2007; Sanderson et al., 2009), evidence-based approaches to veterinary medicine based on level III or IV clinical trials are required to determine the ameliorative effects of VTD. Afflicted patients will then benefit from standard of care.

The aim of this randomized, controlled and double-blinded clinical trial was to determine whether a VTD, which contains high level of omega-3 (1.08% of eicosapentaenoic and docosahexaenoic acid) from fish origin (rainbow trout; *Onchorynchus mykiss*), improves the functional disability of lame privately owned dogs afflicted by OA. We hypothesized that the continuous intake of a VTD rich in omega-3 should improve the limb function to a greater extent than would a control diet devoid of the active nutrient (omega-3). A quantitative measure of functional outcome as provided by the recording of the peak of the vertical ground reaction force (PVF) and a case-specific outcome measures (CSOM) (Gingerich and Strobel, 2003; Lascelles et al., 2008) were used to further validate the use of this VTD as an effective therapeutic approach.

Materials and methods

Experimental design

A randomized, controlled and double-blinded clinical trial was undertaken to evaluate the efficacy of a VTD rich in omega-3. This trial was approved by the Institutional Animal Care and Use Committee in accordance with the guidelines of the Canadian Council on Animal Care. All owners gave informed consent for their participation in the trial. They were also requested to avoid any intense activities (jumping, running, throwing ball or Frisbee, etc.) potentially deleterious for their OA dogs during the study duration.

Sample size was estimated according to previous work done in similar conditions (Moreau et al., 2007). Thirty privately owned dogs diagnosed with OA were randomly allocated to 2 groups of 15 dogs each. A restricted randomization process (random allocation rule) was used to ensure equal group sizes at the end of the trial. Treatment sequence was determined using computer-generated random number. Therapeutic group, hereafter-coded VTD (JM Joint mobility; Nestlé Purina PetCare Company, St. Louis, MO, USA) was a commercially available therapeutic diet formulated for dogs with OA.

The control group, hereafter-coded CTR (experimental formulation; Nestlé Purina PetCare Company) was an experimentally diet formulated to be similar in nutritional content to the VTD, at the exception of the omega-3 content. The CTR was considered as a regular diet. The feeding guideline for both diets was based upon the following equation: Maintenance energy requirement = 100× (body weight (BW) [Kg])$^{0.75}$. During the study, the daily amount of diet was divided into two meals. Incomplete feed uptake was documented. An adaptation phase of 3 days to gradually acclimate dogs to the diets was considered, beginning at day 1. During this adaptation phase, the amount of diet was 20%, 40% and 80% in the first 3 days and then 100% until study completion. Owners were asked to respect good nutritional habit, avoiding any other food than the tested-diets. The VTD diet contained 1.08% of eicosapentaenoic and docosahexaenoic acid as active nutrients (Table 1). Dogs were weighted at Baseline, Week 7 and 13.

Table 1 Summary of the diet's content based on dry matter basis

Nutrients	VTD*	CTR†
Protein (%)	33.9	34.4
Carbohydrate (%)	41.5	41.6
Fat (%)	15.1	15.1
Glucosamine (%)	0.1	0.1
Dietary fatty acids, % dry matter		
Linoleic acid (C18:2n6)	1.69	2.28
Gamma linolenic acid (C18:3n6)	0.02	0.02
Arachidonic acid (C20:4n6)	0.12	0.12
Linolenic acid (C18:3n3)	0.12	0.10
Eicosapentaenoic acid (C20:5n3)	0.53	0.03
Docosahexaenoic acid (C22:6n3)	0.55	0.04
Total long-chain polyunsaturated omega-6 fatty acids (omega-6)	1.86	2.43
Total long-chain polyunsaturated omega-3 fatty acids (omega-3)	1.47	0.18
Omega-6 /omega-3 ratio	1.3	13.6
Eicosapentaenoic and docosahexaenoic acid (%)	1.08	0.07

*VTD Veterinary therapeutic diet.
†CTR Control diet.

Animal selection

Adult (>12 months) dogs weighing >20 kg having radiographic evidence of OA (see computed radiographs section) at the hip or stifle joints were eligible to the clinical trial. Clinical signs of osteoarthritis, including pain or restricted motion upon orthopaedic examination of the hip or stifle were confirmed by a certified veterinary surgeon (Lussier). To be eligible, dogs had to have a decrease in the normal mobility and function of a limb (i.e. lameness) that was visually observed at the level of the hindlimb. The elbows as well as others joints had to be normal upon orthopaedic examinations.

Exclusion criteria were as follows: dogs undergoing surgery for a cranial cruciate ligament rupture (CCLR) within 1 year prior to study initiation, dogs receiving a natural health product (including omega-3) supplement or a VTD for OA management 6 weeks prior to study initiation and dogs receiving NSAID 4 weeks prior to study initiation. Pregnant bitches, dogs having received polysulphated glycosaminoglycans or corticosteroids at any time before study initiation and those suffering from neurologic or other musculoskeletal lesions were excluded. Dogs that underwent orthopaedic surgery within the past year and dogs with CCLR having gross instability (positive drawer motion) were not eligible.

Peak vertical force measurement

Measurements were performed at Baseline, Week 7 and 13 at the trot (speed 1.9–2.2 m/s, acceleration ± 0.5m/s^2) using a force platform, as previously described (Moreau et al., 2010). The PVF was reported and defined as the primary outcome of interest. Normalized PVF as percentage of body weight (%BW) from the first five valid trials were used for statistical purposes. To be eligible, dogs must have PVF value less than that of 66%BW which is consistent to minus 1 SD of the value measured in normal dogs (Madore et al., 2007). When bilateral lameness was observed, the hindlimb having the lowest PVF, in accordance with the orthopaedic exam findings, determined which one was selected for evaluation; otherwise the dog was not eligible.

Case-specific outcome measures

At Baseline, all owners were asked to determine between 2 and 5 activities of daily living that were the most impaired (Gingerich and Strobel, 2003; Lascelles et al., 2008) by the disease. Owner determined each activity according to his own perception of what characterizes the disability of his dog. Activities were then scored on a five-point scale of severity (0–4) as follows: No problem (0), minor disability (1), moderate disability (2), severe disability (3) and complete incapacity (4). A score of 0 cannot be attributed at Baseline. Each activity was assessed twice weekly using a specific form that was kept at home by the owner. For each dog, the median of the scores was determined for all evaluations (total of 27 evaluations).

Computed radiographs

For all dogs, computed radiographs (hips, stifles and elbows) were systematically obtained under sedation as described (Moreau et al., 2010). All radiographs were reviewed by a certified veterinary surgeon (Lussier). The presence of radiographic evidences of OA (osteophytes, enthesiophyte and sclerosis) exclusively observed at the level of the stifle or hip was a prerequisite for inclusion. Dogs with elbow abnormalities graded as borderline (i.e. between normal and grade 1 elbow dysplasia according to the International elbow working group standardized screening procedure) were eligible. Eligible dogs were free of forelimb muscular atrophy, pain or lameness during the orthopaedic examination.

Statistical analyses

Per trial PVF (log-transformed) data were analysed with a repeated-measures general linear mixed model that evaluated the fixed effects of Time (temporal evolution), Group (diets) and the Time × Group interaction, with trials (PVF) and dogs nested in treatment group as random effects. A second linear mixed model was conducted on PVF data (log-transformed) for the difference between Week 13 and Baseline. The mean of the five trials was used and tested for Group as a fixed effect. Body weight was analysed similarly to the first linear model used for PVF, excluding Week 7 data. When necessary, the best covariance structure for fixed and random effects was chosen (Littell et al., 2000) and included in the model. A repeated-measures generalized linear model was used to analyse CSOM data (median of the score given to each selected activities) under Poisson distribution function to evaluate the fixed effects of Time (temporal evolution), Group (diets) and the Time × Group interaction. Scale factor was estimated by Pearson's chi-square. All *post hoc* analyses were performed with appropriate Bonferroni adjustments. For CSOM,

post hoc analyses were performed to compare both groups at the 1st, 13th and 27th assessments. Also, in each groups, assessments (from the 2nd to the 27th) were exclusively compared with Baseline (1st). Significant level was set at $p < 0.05$. Data are presented as mean ± SD. The last-observation-carried-forward approach was applied in the event of missing data. Statistical analyses and graphics were carried out using SPSS Statistics software, version 17.0 (SPSS Inc, Chicago, IL USA) and SIGMAPLOT, version 10.0 (Systat software Inc, Chicago, IL, USA) respectively.

Results

Animal description

Characteristics of the study cohort are presented (Table 2). Lameness was confirmed by recording abnormally low PVF using a force platform. Owners reported reluctance to perform daily life activity as recorded during CSOM. Daily feed uptake was reduced when a gain in BW >1 kg occurred. Feed uptake was reduced in two CTR-fed dogs (by 20 and 12.5% respectively) and in three VTD-fed dogs (by 33, 12.5 and 12.5% respectively). Significant difference was not observed within and among groups for the level of BW (Group effect; $p = 0.166$, Time effect; $p = 0.079$, Time × Group interaction; $p = 0.805$).

Missing data

A patient lost to follow-up occurred in the CTR group because the owner lost his dog during the study. A patient lost to follow-up occurred in the VTD group when an owner decided to withdraw his dog from the trial for personal reasons unrelated to the study. Also in this group, a CSOM form was lost by the owner, meaning that only the initial data were accessible.

Primary study outcome: peak vertical force

In dogs, the PVF represents the force generated by the painful limb during the stance phase of the stride. The dispersion of data for the recording of the PVF for each group at each time session is illustrated (Fig. 1). The PVF was increased over time (Time effect; $p < 0.001$) without a significant Group effect ($p = 0.147$). Groups evolved differently over time (Time × Group interaction; $p = 0.006$). According to *post hoc* analyses, PVF at Week 7 (58.4 ± 8.0%BW, $p < 0.001$) and at Week 13 (59.5 ± 8.5%BW, $p < 0.001$) was higher than Baseline (56.0 ± 7.3%BW) in VTD fed dogs. From Week 7 to 13, PVF did not increase significantly ($p = 0.457$). In control dogs, PVF at Week 7 (54.0 ± 9.6%BW) and at Week 13 (53.8 ± 10.5%BW) were not significantly increased compared with Baseline (53.3 ± 8.3% BW, $p = 0.999$). There was no significant difference between CTR and VTD groups at Baseline, Week 7 and at Week 13. Figure 2 presents the individual change in PVF recorded at Week 13. From Baseline to Week 13, VTD-fed dogs had a mean change of 3.5 ± 6.8%BW. This change was not significantly different

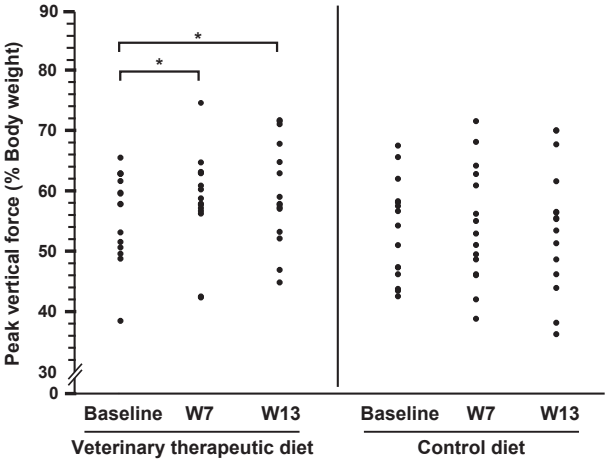

Fig. 1 Individual dot plot of peak vertical force recorded in privately owned dogs with naturally occurring osteoarthritis after 7 and 13 weeks of feeding either Control diet or a Veterinary therapeutic diet rich in omega-3. Dots are PVF recorded in each dog (15 dogs per group, per time). *Significantly different compared with Baseline $p < 0.05$.

Table 2 Characteristics of the dogs

Groups	Age (year)	Male dog/ total dog	Body weight (kg)		
			Baseline	Week 7	Week 13
CTR*	6.6 (3.3)	12/15	41.0 (8.2)	40.8 (8.0)	40.4 (8.2)
VTD†	6.4 (2.7)	8/15	36.7 (12.3)	36.6 (12.5)	36.4 (12.6)

Data are presented as mean (SD). 15 dogs per group.

*CTR Control diet.

†VTD Veterinary therapeutic diet.

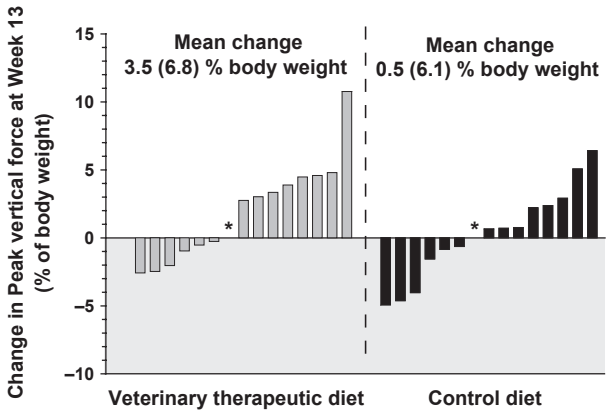

Fig. 2 Individual changes in peak vertical force recorded in privately owned dogs with naturally occurring osteoarthritis after 13 weeks of feeding either Control diet or a Veterinary therapeutic diet rich in omega-3. Mean (SD) changes were the difference between Week 13 vs. Baseline. *Incomplete data were managed using last-data-carried-forward method. Grey zone represent negative change (i.e. deterioration).

compared with the one of CTR-fed dogs (0.5 ± 6.1%BW, p = 0.211).

Case-specific outcome measures

The CSOM recorded the owners' assessment of the severity of daily life impairment in their dogs based upon preselected activities reported to be problematic and painful. For CSOM, a lower value means better activity performance.

The evolution of the CSOM is illustrated (Fig. 3). There was a decrease in CSOM over time (Time effect; $p < 0.001$), without a significant Group effect ($p = 0.245$). Groups evolved differently over time (Time × Group; $p < 0.001$). Hence, *post hoc* analyses did not reveal a significant decrease in CSOM for CTR-fed dogs when compared to Baseline. Conversely, significant decreases in CSOM were observed for VTD-fed dogs at the 25th ($p = 0.047$), 26th ($p = 0.047$) and 27th ($p = 0.047$) assessments (Fig. 2). There was no significant difference between CTR and VTD groups for the selected assessments.

Discussion

This clinical trial evaluated the functional outcomes of lame privately owned dogs afflicted by OA following a 13 weeks of feeding with a VTD containing high levels of omega-3. According to the primary study outcome (PVF), OA dogs were significantly improved ($p < 0.001$) 7 weeks after the beginning of a dietary modulation. The improvement in the functional disability was maintained through the 13 weeks duriation, achieving a mean improvement of 3.5 ± 6.8%BW when compared to initial limb support ($p < 0.001$). When expressed relatively to Baseline (pre-treatment) values, the improvement corresponded to 6.9 ± 12.2%. The ameliorative effect of VTD was in accordance with previous trials performed by our group (Moreau et al., 2003, 2004, 2007) and others (Budsberg et al., 1999) using NSAID and a powder of elk velvet antler. Moreover, the level of improvement represented an increment of 1.4 kg applied on the afflicted and painful limb for a dog of 36.7 kg. The effect size of the VTD improvement was 0.5, which was consistent with a moderate therapeutic effect (Cohen, 1992).

The primary study outcome was identified as PVF that reflects the maximal limb support recorded

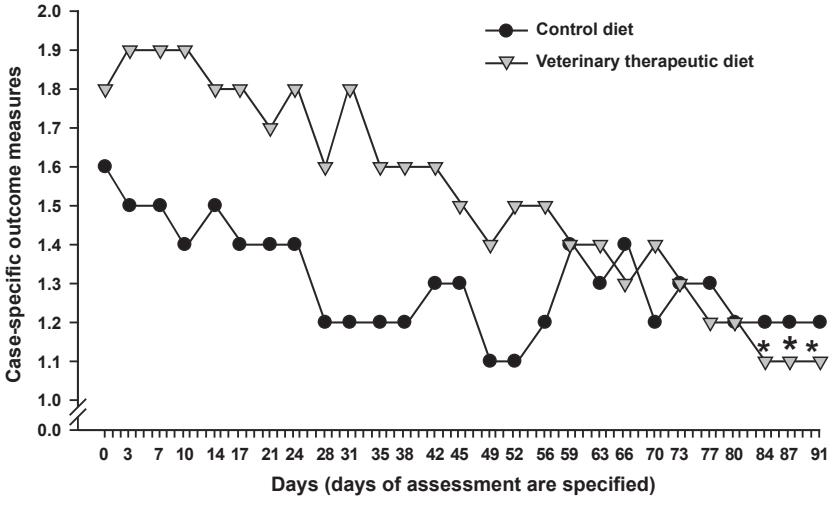

Fig. 3 Temporal evolution of the CSOM recorded in privately owned dogs with naturally occurring osteoarthritis after 7 and 13 weeks (W) of feeding either Control diet or a Veterinary therapeutic diet rich in omega-3. Assessments were performed twice weekly. Each data point represents the mean (15 dogs per group, per assessment). *Significantly different compared with Baseline $p < 0.05$.

during the stance phase of the stride. Recording of the PVF has been shown to express low coefficient of variation in OA dogs (Madore et al., 2007). Among all data recorded by a force platform, *a priori* determination of a primary outcome ensures good practice of clinical trial reporting (Budsberg, 1997). Hence, to avoid a high rate of type I error because of multiple tests and to avoid searching for significant data, it was established to focus only on PVF instead of analysing all force platform data.

On the basis of the subjective assessment, an improvement was also observed in dogs fed a diet rich in omega-3 following over a 13-week period ($p = 0.047$). Hence, owners of VTD-fed dogs recognized that their dog had better performance in activities of daily living determined to be impaired by the painful disease. The determination of abnormal behaviour potentially linked to pain is believed to represent a key point in the management of OA (Hellyer et al., 2007). In this way, the VTD was able to improve the quality of life by reducing the daily disability.

The limb impairment was improved in dogs fed the VTD according to the primary study outcome ($p < 0.001$). However, our hypothesis was not supported: the magnitude of the change in the VTD group ($3.5 \pm 6.8\%$BW) did not statistically exceed the one of the CTR group ($0.5 \pm 6.1\%$BW). In addition, as illustrated in Fig. 2, 8/15 (53%) CTR-fed dogs had an increase in PVF at Week 13. Therefore, the present study cannot convincingly claim that VTD improved the limb function to a greater extent than a regular diet used as negative (placebo) control. We believed that the positive change observed in several CTR fed dogs, and consequently, the large data variation has altered the statistical power necessary to support our hypothesis. According to sample size estimate, it appears that 73 dogs per group are necessary to achieve 80% power to detect a significant difference between $3.5 \pm 6.8\%$BW vs. $0.5 \pm 6.1\%$BW.

In the present study, the use of a regular diet given under strict feeding guidelines provided a favourable response in some CTR fed dogs. These findings were consistent with the better limb function observed in a large proportion of dogs (38%) (Roush et al., 2010) as well as to the reduction in carprofen dosage in dogs fed a regular diet (Fritsch et al., 2010). The natural fluctuation in disease severity (maturation effect) upon force platform measurement is presently not fully documented in placebo-treated dogs. In a manner to optimize the design of clinical trial, it is necessary to better document the evolution of OA dogs as to whether or not their functional outcome remain stable over time.

Exacerbation of lameness related to a gain in BW was previously demonstrated using force platform to record peak vertical force, while benefits occurred when BW was decreased (Moreau et al., 2010). In the present study, the BW of the dogs in their respective group was not modified when both diets were administered according to strict and balanced feeding guidelines. As OA dogs are mostly sedentary, it is crucial that maintenance energy requirement be adjusted accordingly.

The present study has been conducted based on the following limitations: (i) Data were limited to dogs with hindlimb OA and cannot necessarily be extrapolated to those being afflicted at other sites. (ii) The study duration is limited to 13 weeks, while OA is a chronic persistent condition. (iii) The study cohort was selected based on force platform measurement that may be unrepresentative of the clinical portrait of OA in dogs. (iv) The present study examined the effect of a VTD as a monotherapy even though canine OA treatment is multimodal. (v) Intense activities were reported to be deleterious in dogs afflicted by OA (Beraud et al., 2010). Avoiding intense activity may therefore have precluded to a bias in the study outcome. In addition, whether or not an increment in PVF similar to what observed in VTD-fed dogs ($3.5 \pm 6.8\%$BW) is clinically relevant or simply a statistical artefact remains to be challenged. Hence, despite the fact that force platforms are widely used in the orthopaedic field, guidelines to ensure adequate data management, interpretation and translation to clinical setting are still lacking.

On the basis of clinical evidences from objective functional outcome and continuous owner's assessments, the use of a VTD that contains high level of omega-3 from fish origin could be considered as a component in the multimodal management of canine OA.

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References

Aragon, C. L.; Hofmeister, E. H.; Budsberg, S. C., 2007: Systematic review of clinical trials of treatments for osteoarthritis in dogs. *Journal of the American Veterinary Medical Association* **230**, 514–521.

Bauer, J. E., 2007: Responses of dogs to dietary omega-3 fatty acids. *Journal of the American Veterinary Medical Association* **231**, 1657–1661.

Beraud, R.; Moreau, M.; Lussier, B., 2010: Effect of exercise on kinetic gait analysis of dogs afflicted by osteoarthritis. *Veterinary and Comparative Orthopaedics and Traumatology* **23**, 87–92.

Biondo, P. D.; Brindley, D. N.; Sawyer, M. B.; Field, C. J., 2008: The potential for treatment with dietary long-chain polyunsaturated n-3 fatty acids during chemotherapy. *Journal of Nutritional Biochemistry* **19**, 787–796.

Brown, S. A.; Brown, C. A.; Crowell, W. A.; Barsanti, J. A.; Kang, C. W.; Allen, T.; Cowell, C.; Finco, D. R., 2000: Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. *Journal of Laboratory and Clinical Medicine* **135**, 275–286.

Budsberg, S. C., 1997: Outcome assessment in clinical trials involving medical management of osteoarthritis in small animals. *The Veterinary Clinics of North America Small Animal Practice* **27**, 815–823.

Budsberg, S. C.; Johnston, S. A.; Schwarz, P. D.; DeCamp, C. E.; Claxton, R., 1999: Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. *Journal of the American Veterinary Medical Association* **214**, 206–210.

Cohen, J., 1992: A power primer. *Psychological Bulletin* **112**, 155–159.

Folador, J. F.; Karr-Lilienthal, L. K.; Parsons, C. M.; Bauer, L. L.; Utterback, P. L.; Schasteen, C. S.; Bechtel, P. J.; Fahey, G. C. Jr, 2006: Fish meals, fish components, and fish protein hydrolysates as potential ingredients in pet foods. *Journal of animal science* **84**, 2752–2765.

Fritsch, D. A.; Allen, T. A.; Dodd, C. E.; Jewell, D. E.; Sixby, K. A.; Leventhal, P. S.; Brejda, J.; Hahn, K. A., 2010: A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis. *Journal of the American Veterinary Medical Association* **236**, 535–539.

Gingerich, D. A.; Strobel, J. D., 2003: Use of client-specific outcome measures to assess treatment effects in geriatric, arthritic dogs: controlled clinical evaluation of a nutraceutical. *Veterinary Therapeutics* **4**, 376–386.

Hansen, R. A.; Harris, M. A.; Pluhar, G. E.; Motta, T.; Brevard, S.; Ogilvie, G. K.; Fettman, M. J.; Allen, K. G., 2008: Fish oil decreases matrix metalloproteinases in knee synovia of dogs with inflammatory joint disease. *Journal of Nutritional Biochemistry* **19**, 101–108.

Hellyer, P.; Rodan, I.; Brunt, J.; Downing, R.; Hagedorn, J. E.; Robertson, S. A., 2007: AAHA/AAFP pain management guidelines for dogs & cats. *Journal of the American Animal Hospital Association* **43**, 235–248.

Johnston, S. A., 1997: Osteoarthritis. Joint anatomy, physiology, and pathobiology. *The Veterinary Clinics of North America Small Animal Practice* **27**, 699–723.

Kirby, N. A.; Hester, S. L.; Rees, C. A.; Kennis, R. A.; Zoran, D. L.; Bauer, J. E., 2009: Skin surface lipids and skin and hair coat condition in dogs fed increased total fat diets containing polyunsaturated fatty acids. *Journal of Animal Physiology and Animal Nutrition* **93**, 505–511.

Lascelles, B. D.; Gaynor, J. S.; Smith, E. S.; Roe, S. C.; Marcellin-Little, D. J.; Davidson, G.; Boland, E.; Carr, J., 2008: Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. *Journal of Veterinary Internal Medicine* **22**, 53–59.

Laurent, G.; Moe, G.; Hu, X.; Holub, B.; Leong-Poi, H.; Trogadis, J.; Connelly, K.; Courtman, D.; Strauss, B. H.; Dorian, P., 2008: Long chain n-3 polyunsaturated fatty acids reduce atrial vulnerability in a novel canine pacing model. *Cardiovascular Research* **77**, 89–97.

LeBlanc, C. J.; Horohov, D. W.; Bauer, J. E.; Hosgood, G.; Mauldin, G. E., 2008: Effects of dietary supplementation with fish oil on in vivo production of inflammatory mediators in clinically normal dogs. *American Journal of Veterinary Research* **69**, 486–493.

Littell, R. C.; Pendergast, J.; Natarajan, R., 2000: Modelling covariance structure in the analysis of repeated measures data. *Statistics in Medicine* **19**, 1793–1819.

Madore, E.; Huneault, L.; Moreau, M.; Dupuis, J., 2007: Comparison of trot kinetics between dogs with stifle or hip arthrosis. *Veterinary and Comparative Orthopaedics and Traumatology* **20**, 102–107.

Miller, W. H.; Scott, D. W.; Wellington, J. R., 1992: Treatment of dogs with hip arthritis with a fatty acid supplement. *Canine Practice* **17**, 6–8.

Moreau, M.; Dupuis, J.; Bonneau, N. H.; Desnoyers, M., 2003: Clinical evaluation of a nutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *The Veterinary Record* **152**, 323–329.

Moreau, M.; Dupuis, J.; Bonneau, N. H.; Lecuyer, M., 2004: Clinical evaluation of a powder of quality elk velvet antler for the treatment of osteoarthrosis in dogs. *The Canadian Veterinary Journal* **45**, 133–139.

Moreau, M.; Lussier, B.; Doucet, M.; Vincent, G.; Martel-Pelletier, J.; Pelletier, J. P., 2007: Efficacy of licofelone in dogs with clinical osteoarthritis. *The Veterinary Record* **160**, 584–588.

Moreau, M.; Troncy, E.; Bichot, S.; Lussier, B., 2010: Influence of changes in body weight on peak vertical force in osteoarthritic dogs: a possible bias in study outcome. *Veterinary Surgery* **39**, 43–47.

Roush, J. K.; Cross, A. R.; Renberg, W. C.; Dodd, C. E.; Sixby, K. A.; Fritsch, D. A.; Allen, T. A.; Jewell, D. E.; Richardson, D. C.; Leventhal, P. S.; Hahn, K. A., 2010:

Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. *Journal of the American Veterinary Medical Association* **236**, 67–73.

Sanderson, R. O.; Beata, C.; Flipo, R. M.; Genevois, J. P.; Macias, C.; Tacke, S.; Vezzoni, A.; Innes, J. F., 2009: Systematic review of the management of canine osteoarthritis. *The Veterinary Record* **164**, 418–424.