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Dose-Titration Effects of Fish Oil in Osteoarthritic Dogs

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Background: Food supplemented with fish oil improves clinical signs and weight bearing in dogs with osteoarthritis (OA).

Objective: Determine whether increasing the amount of fish oil in food provides additional symptomatic improvements in OA.

Animals: One hundred and seventy-seven client-owned dogs with stable chronic OA of the hip or stifle.

Methods: Prospective, randomized clinical trial using pet dogs. Dogs were randomly assigned to receive the baseline therapeutic food (0.8% eicosopentanoic acid [EPA] + docosahexaenoic acid [DHA]) or experimental foods containing approximately 2- and 3-fold higher EPA+DHA concentrations. Both veterinarians and owners were blinded as to which food the dog received. On days 0, 21, 45, and 90, serum fatty acid concentrations were measured and veterinarians assessed the severity of 5 clinical signs of OA. At the end of the study (day 90), veterinarians scored overall arthritic condition and progression of arthritis based on their clinical signs and an owner interview.

Results: Serum concentrations of EPA and DHA rose in parallel with food concentrations. For 2 of 5 clinical signs (lameness and weight bearing) and for overall arthritic condition and progression of arthritis, there was a significant improvement between the baseline and 3X EPA+DHA foods (P=.04, .03, .001, .0008, respectively) but not between the baseline and the 2X EPA+DHA foods.

Conclusions and Clinical Importance: Increasing the amount of fish oil beyond that in the baseline food results in dose-dependent increases in serum EPA and DHA concentrations and modest improvements in the clinical signs of OA in pet dogs.

Key words: Canine; fatty acid; Osteoarthritis.

Osteoarthritis (OA) is one of the most common chronic musculoskeletal diseases and is believed to be a leading cause of pain and lameness in dogs.[1] In the United States, an estimated 20% of dogs 1 year of age or older has radiographic signs of OA.[2] OA is generally a chronic, progressive disease characterized by the degeneration of articular cartilage with loss of proteoglycan and collagen, subchondral bone sclerosis, periarticular proliferation of new bone, and chronic inflammation of the synovial membrane. These changes occur secondary to acquired or congenital musculoskeletal disorders such as hip dysplasia.[1]

Management of OA includes prevention, slowing progression of the disease, and controlling clinical signs.[1,3] Proper nutrition, weight control, controlled exercise, physical therapy, anti-inflammatory and analgesic medications, and other disease-modifying agents are often part of the treatment strategy. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are effective, but systemic use of NSAIDs can have adverse effects, including gastrointestinal ulceration, renal failure, hepatic failure, and death,[4] and the long-term use of NSAIDs and corticosteroids can accelerate cartilage degeneration.[5,6]

A variety of recent human clinical studies[7–12] and a meta-analysis[13] found that dietary supplementation with fish oil, which is enriched in omega-3 fatty acids (FAs), especially eicosopentanoic acid (EPA) and docosahexaenoic acid (DHA),[14] provides benefits in rheumatoid arthritis. This might be due to the ability of omega-3 FAs to lower arachidonic acid (AA) concentrations and alter the production of eicosanoids to less inflammatory forms.[15] In addition, omega-3 FAs reduce the expression of cartilage-degrading enzymes, cyclooxygenase-2, and inflammation-inducible cytokines.[16] Feeding fish oil reduces the concentrations of inflammatory factors in a mouse model of rheumatoid arthritis,[17] and oral administration of EPA and DHA reduces streptococcal cell wall-induced arthritis in Lew/SSN rats.[18]

Although the pathophysiology of rheumatoid arthritis and OA differ, both have an inflammatory aspect that could be sensitive to omega-3 FAs.[1] Food supplemented with fish oil to provide 0.8% EPA+DHA improves weight bearing and owner- and veterinarian-assessed clinical signs in dogs with OA.[19,20] Here, we evaluated whether further increases in the dietary content of fish oil provides additional symptomatic improvement in OA.

Abbreviations:

AA	arachidonic acid
ALA	α-linolenic acid
DHA	docosahexaenoic acid
EPA	eicosopentanoic acid
FA	fatty acid
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis

Materials and Methods

Study design

This was a prospective, randomized, blinded study using pet dogs in the home setting recruited at 27 privately owned veterinary

From Hill's Pet Nutrition Inc, Topeka, KS (Fritsch, Allen, Dodd, Jewell, Sixby, Hahn); and 4Clinics, Paris, France (Leventhal). Animals were recruited from 27 privately owned veterinary hospitals in the United States, and analyses were carried out at Hill's Pet Nutrition Inc, Topeka, KS.

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hospitals in the United States. All aspects of this trial were conducted in strict accordance with Hill's Pet Nutrition Inc. Global Animal Welfare Policy and were approved by the sponsor's Institutional Animal Care and Use Committee. All pet owners gave informed written consent. Clinics and primary care veterinarians volunteered to participate in the study and were approved for inclusion on the basis of a site visit to ensure sufficient quality of care.

Adult dogs with clinical signs and radiographic changes consistent with OA in the hip or stifle were considered candidates for the study. Investigators were required to take 2 radiographs (ventral/dorsal and lateral) of the affected joint, which they used to verify a diagnosis of OA according to standard criteria.[21] Dogs were included if they currently consumed dry food; were 1 year of age or older; had a body condition score (BCS) >1 (1, very thin; 2, underweight; 3, ideal; 4, overweight; 5, obese); had radiographic evidence of OA in the hip or stifle and any signs of lameness; had a consistent dosing regimen for at least 30 days if on medications or supplements; and were otherwise healthy based on a physical exam, complete blood count, serum chemistry panel, and urinalysis.

Exclusion criteria were as follows: Acute traumatic injuries (including acute OA), systemic illness or other bone or joint disease that might have interfered with or prevented the evaluation of the dog's response, arthrocentesis within 30 days, intra-articular injection of any material into any joint within 90 days, surgery on any joint within 180 days, planned surgery during the study, pregnant, or fractious behavior. Dogs were dismissed during the course of the study for the following reasons: adverse reaction, injury, or illness warranting treatment and/or surgical intervention that prevented compliance with study protocol and/or required unmasking of the experimental treatment; the investigator (primary care veterinarian) became unmasked; the investigator determined that the dog was unable to continue in the study due to excessive pain, other complications of OA, or concurrent medical conditions; the dog's owner did not comply with study restrictions or withdrew the dog from the study; the dog was lost to follow-up, died, or was euthanized. Finally, dogs were removed from the analysis if it was determined ex post facto that they did not meet eligibility criteria.

Study Foods

Food A was a commercially available therapeutic diet that contains fish oil.[a] Foods B and C included additional marine oil concentrate for dry food and menhaden oil for wet food.[b] The amount of flaxseed oil was reduced in foods B and C to maintain a constant protein level and similar fat levels. Nutrient profiles were assessed using standard methods by Eurofins (Des Moines, IA). All foods met or exceeded the complete and balanced nutrition guidelines of the Association of American Feed Control Officials for the maintenance of adult (>1 year) dogs.[22]

Study Conduct

A random sequence of the 3 diets was generated for 21 potential participants each at 40 potential clinics using PROC PLAN in SAS version 9.1.3,[c] with the requirement that equal numbers of diets had to be dispensed at each clinic. As a dog was enrolled in the study, it was assigned to the first available diet in the randomization sequence for the designated clinic. Investigators (primary care veterinarians) and dog owners were masked to the identity of the study foods.

Pet owners were given the option of feeding their dogs wet only, dry only, or a combination of wet and dry food. Owners were instructed to transition dogs to the new food over a period of 3 days by mixing increasing amounts of study food with decreasing amounts of the food used before entry into the study. The amount fed was increased or decreased according to the dog's weight at subsequent visits. The feeding period for each dog continued for 90 days from the start date of the test. Dogs were maintained in the owner's households during and following completion of the study. For each dog, the same veterinarian performed all clinical assessments and the assessment at study end for a given case.

At enrollment (day 0), and on days 21, 45, and 90, the investigator (primary care veterinarian) performed a clinical evaluation of the dog, which included a complete medical history (including drug history), a complete physical examination (system review), and an orthopedic examination. Owners were asked to fast their dogs overnight before the visit. For the orthopedic examination, a score of 1–4 (1, none; 2, mild; 3, moderate; 4, severe) was assigned to the following 5 signs: lameness, reluctance to bear weight in the affected limb, reduction in range of motion of the affected limb, reluctance to hold up the contralateral limb, and pain on palpation of the affected joint. Investigators did not solicit input from pet owners before assigning these scores. The scoring systems used here were similar to those described in our previous studies.[19,20]

At study completion (day 90), investigators were asked to answer 2 questions assessing the overall changes in the clinical condition of the dog compared with day 0: (1) "Based on the pet owner's input and your own clinical assessment, how would you describe the impact the study food has had on this dog's arthritic condition? (1, significantly slowed progression of the arthritis; 2, slightly slowed progression of the arthritis; 3, no effect; 4, slightly accelerated progression of the arthritis; 5, significantly accelerated progression of the arthritis)" and (2) "Based on the pet owner's input and your own clinical assessment, how has the arthritic condition of this dog changed since eating the study food? (1, extreme improvement; 2, moderate improvement; 3, slight improvement; 4, no change; 5, slight deterioration; 6, moderate deterioration; 7, extreme deterioration)?"

During the course of the study, all adverse events noticed by the owner or veterinarian or identified from laboratory analyses were recorded. In addition, the veterinarian recorded whether the adverse event was new, its severity, the relatedness to the study food or concomitant medication, the nature of the event, and other relevant details.

At the day 0, 21, 45, and 90 visits, blood was collected for analysis of complete blood count, serum biochemistry, and FAs. Serum concentrations of FAs were analyzed by gas chromatography as described previously.[20]

Statistical Analyses

All calculations were made using SAS version 9.1.3.[c] The sample size was calculated based on an anticipated reduction of 0.25 U in the veterinarian evaluation score for Food B and 0.5 U for Food C, standard deviation of 1.0, significance level of $\alpha=0.05$, minimum desired power level of 0.70, and a dismissal rate of 15%. The sample size calculation indicated that 60 dogs per treatment would be required. Age and weight of the animals on each food were compared using a 1-way analysis of variance (ANOVA). Distributions of BCSs for the 3 groups were compared using the Cochran-Mantel-Haenzel χ^2 test. Sex, reproductive status, primary affected joint (hip or stifle), and concurrent therapies for the 3 groups were compared using exact Pearson's χ^2 tests. Serum FA concentrations were analyzed with a repeated-measures ANOVA using PROC MIXED. A random intercept term was included to account for animal-to-animal variation. Data from veterinarian evaluations were analyzed with a repeated-measures ANOVA using PROC GLIMMIX, using a Poisson distribution and a log-link function. Spatial power, first-order ante-dependence, and unstructured covariance patterns were fit to the data and Akaike's information criteria and the Bayesian information criteria were used to determine the best covariance pattern. The Kenward-Roger procedure was used to adjust the standard errors and test statistics for the presence of random effects and correlated errors in the model. The time main effect was partitioned into linear and quadratic trends using orthogonal polynomial. The method of Snedecor[23] was used to calculate the

coefficients for the unequally spaced intervals. The food × time interaction effect was partitioned into linear and quadratic trends for each food separately using estimate statements. Foods B and C were compared with Food A using a 2-sided Dunnett's test for serum FAs and a 1-sided Dunnett's test for the 5 clinical signs and the 2 overall scores. For both the 5 clinical signs and the 2 overall scores, the 27 clinics involved were considered a random effect, and clinic and clinic × treatment random effect terms were included in the ANOVA model. However, the variance component associated with the clinic × treatment effect was zero in all cases and was therefore dropped from the final model. Similarly, there was no significant medication effect, so it was also dropped from the ANOVA model. A P-value of $<.05$ was considered as indicating statistical significance.

Results

Study Foods

According to a 2 : 1 dry/wet feeding ratio, which was calculated on the basis of the total amount of each food consumed by all dogs in the study (data not shown), the estimated total level of EPA and DHA in foods in Foods A, B, and C, respectively, was 0.8%, 2.0%, and 2.9% on a dry-matter basis and 0.22, 0.53 and 0.75 g/100 kcal (ie, on an energy basis) (Table 1). Thus, the amount of fish oil actually present in Foods B and C was approximately 2- and 3-fold higher than in Food A. There were few changes in the amount of total protein, carbohydrate, and fiber, although the total amount of fat increased progressively in the 3 foods.

Dog Disposition

Two hundred and forty-nine dogs were screened for the study. Of these, 37 were eliminated because they did not meet the inclusion criteria or because they met 1 or more of the exclusion criteria. Reasons for exclusion included a lack of radiographic evidence of arthritis in the hip or stifle (n=18), noncompliance (n=6), a nontargeted form of arthritis (n=6), presence of a concurrent medical condition (n=6), or death (n=1).

Table 1. Nutritional profile of study foods.

Component	Units	Food A	Food B	Food C
Protein	% dry weight	20.0	19.7	19.8
	g/100 kcal	5.5	5.3	5.1
Fat	% dry weight	14.0	16.0	20.8
	g/100 kcal	3.8	4.3	5.3
Carbohydrate	% dry weight	53.5	51.2	45.9
	g/100 kcal	14.7	13.7	11.7
Crude fiber	% dry weight	8.1	8.7	9.1
	g/100 kcal	2.2	2.3	2.3
C18 : 3 (ALA)	% dry weight	2.6	1.5	1.4
	g/100 kcal	0.7	0.4	0.4
C20 : 5 (EPA)	% dry weight	0.45	1.1	1.6
	g/100 kcal	0.12	0.29	0.41
C22 : 6 (DHA)	% dry weight	0.34	0.90	1.35
	g/100 kcal	0.09	0.24	0.34
EPA + DHA	% dry weight	0.79	1.98	2.94
	g/100 kcal	0.22	0.53	0.75
Total omega-6 FAs	% dry weight	2.7	2.4	2.3
	g/100 kcal	0.74	0.65	0.58
Total omega-3 FAs	% dry weight	3.4	3.8	5.0
	g/100 kcal	0.9	1.0	1.3
Omega-3/omega-6 FA ratio	—	1.26	1.57	2.19

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosopentanoic acid; FA, fatty acid.

Contents based on a 2 : 1 dry/wet food feeding ratio.

Table 2. Dog disposition.

	Food A	Food B	Food C
Dogs randomized	71	69	72
Dogs dismissed	16	7	12
Lack of palatability of food	4	2	4
Concurrent medical condition	2	1	2
Owner compliance	1	3	1
Surgery for cranial cruciate ligament rupture	3	0	1
Death or euthanasia	2	0	2
Adverse event	2	1	1
Ineligible ex post facto	2	0	1
Dogs completing the study according to protocol	55	62	60

The remaining 212 dogs were assigned food (Table 2). These dogs were enrolled at 27 clinics, and the number of dogs per clinic ranged from 3 to 13. A total of 35 dogs were dismissed during the course of the study. Of the 177 dogs completing the study according to protocol, 55 received Food A, 62 received Food B, and 60 received Food C.

There were no significant differences in the age, body weight, BCS, affected joint, use of concurrent therapies, sex, or reproductive status between the 3 treatment groups (Table 3). Also, there were no significant differences in body weights or BCS between foods or over time during the course of the study.

Changes in Serum FA Concentrations

Serum FA concentrations were determined at study start (day 0) and on days 21, 45, and 90 after initiation of feeding with the study food (Table 4). There was a significant increase ($P<.001$) in the serum concentrations of individual (EPA, DHA, and α-linolenic acid [ALA]) and total omega-3 FAs over time for all 3 foods. There were also significant decreases ($P<.001$) in individual (C18 : 3, C22 : 4, and AA) and total omega-6 FAs over time for all 3 foods. In all cases, the blood concentrations for all FAs appeared to have stabilized within 45 days. Changes in the serum concentrations of all omega-3 FAs (ALA, EPA, and DHA) and in 2 of the omega-6 FAs (C20 : 2 and AA) were significantly different over time between the baseline commercial food (food A) and the 2 foods with higher concentrations of fish oil (foods B and C). Finally, linear regression analysis showed a strong relationship between the estimated dietary intake of both EPA and DHA and their serum concentrations at study end (day 90) (data not shown).

Table 3. Characteristics of dogs completing the study according to protocol.

Characteristics	Food A (n=55)	Food B (n=62)	Food C (n=60)	*P*-value
Age at study start (years)	8.3 ± 3.4	8.6 ± 3.4	8.7 ± 3.7	.77
Weight (kg)				
Day 0 (mean ± SD)	31.8 ± 14.3	32.3 ± 12.3	31.7 ± 10.7	.97
Day 90 (mean ± SD)	31.6 ± 13.7	32.9 ± 12.5	31.7 ± 10.9	.81
Change (mean ± SD)	−0.26 ± 2.43	0.61 ± 2.14	0.01 ± 3.87	.25
BCS (score [1–5])				
Day 0 (mean ± SD)	3.38 ± 0.83	3.50 ± 0.72	3.50 ± 0.72	.63
Day 90 (mean ± SD)	3.35 ± 0.75	3.49 ± 0.60	3.43 ± 0.67	.51
Change (mean ± SD)	−0.04 ± 0.64	−0.02 ± 0.54	−0.07 ± 0.48	.71
Sex				.34
Total female, n (%)	28 (51)	39 (63)	31 (52)	
Total male, n (%)	27 (49)	23 (37)	29 (48)	
Reproductive status				.88
Intact	5 (9)	4 (6)	4 (7)	
Neutered/Spayed	50 (91)	58 (94)	56 (93)	
Primary-affected joint at study start				.99
Hip, n (%)	40 (73)	45 (73)	44 (73)	
Stifle, n (%)	15 (27)	17 (27)	16 (27)	
Concurrent therapy				.36
None, n (%)	13 (24)	15 (24)	20 (33)	
Prescription NSAIDs, n (%)	19 (35)	13 (21)	16 (27)	
Glycosaminoglycans, n (%)	8 (15)	8 (13)	9 (15)	
Combination of concurrent therapies, n (%)	15 (27)	26 (42)	15 (25)	

BCS, body condition score; SD, standard deviation.

Change in Severity of Clinical Parameters as Assessed by Investigators

Investigators (primary care veterinarians) performed an orthopedic evaluation of dogs on days 0, 21, 45, and 90 (Table 5). The severity of 5 signs was scored on a 4-point scale (1 for none to 4 for severe).[19,20] ANOVA indicated that the effects of the treatments did not significantly vary between the clinics and were not significantly influenced by the presence of concurrent

Table 4. Serum FA concentrations for dogs completing the study according to protocol.

FA	Food	Day 0	Day 21	Day 45	Day 90	*P* Versus Food A
Omega-3 FAs						
C18 : 3 (ALA)	A	1.33 ± 0.16	5.77 ± 0.37	5.47 ± 0.34	5.90 ± 0.34	
	B	1.31 ± 0.15	3.40 ± 0.33	3.98 ± 0.32	3.68 ± 0.32	<.0001
	C	1.28 ± 0.14	2.93 ± 0.34	3.32 ± 0.32	3.29 ± 0.32	<.0001
C22 : 6 (DHA)	A	3.50 ± 0.55	13.7 ± 0.72	13.7 ± 0.79	13.9 ± 0.73	
	B	4.70 ± 0.51	18.6 ± 0.65	19.4 ± 0.72	19.8 ± 0.67	<.0001
	C	3.90 ± 0.49	21.0 ± 0.66	21.6 ± 0.74	22.7 ± 0.68	<.0001
C20 : 5 (EPA)	A	1.29 ± 0.43	18.7 ± 1.5	18.6 ± 1.6	19.6 ± 1.6	
	B	1.56 ± 0.40	26.5 ± 1.3	29.1 ± 1.5	29.3 ± 1.5	<.0001
	C	1.86 ± 0.39	34.5 ± 1.4	35.8 ± 1.5	39.2 ± 1.5	<.0001
Total	A	6.08 ± 0.93	38.1 ± 2.2	37.8 ± 2.4	39.5 ± 2.4	
	B	7.57 ± 0.87	48.6 ± 2.0	52.6 ± 2.2	52.7 ± 2.2	<.0001
	C	6.99 ± 0.84	58.4 ± 2.1	60.7 ± 2.3	65.1 ± 2.2	<.0001
Omega-6 FAs						
C18 : 3	A	0.36 ± 0.03	0.15 ± 0.03	0.14 ± 0.03	0.18 ± 0.03	
	B	0.30 ± 0.02	0.13 ± 0.02	0.18 ± 0.02	0.16 ± 0.02	.53
	C	0.27 ± 0.02	0.09 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	.08
C20 : 4 (AA)	A	75.4 ± 2.8	51.0 ± 1.7	46.9 ± 1.9	47.3 ± 1.6	
	B	73.6 ± 2.5	41.9 ± 1.6	39.8 ± 1.7	37.6 ± 1.5	.003
	C	70.3 ± 2.5	37.5 ± 1.6	36.9 ± 1.7	35.2 ± 1.9	<.0001
Total	A	149.9 ± 5.1	114.6 ± 3.5	109.8 ± 4.1	112.5 ± 3.6	
	B	144.8 ± 4.7	94.3 ± 3.2	97.1 ± 3.8	92.2 ± 3.3	.003
	C	140.8 ± 4.7	79.9 ± 3.3	82.6 ± 3.9	81.7 ± 3.4	<.0001

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosopentanoic acid; FA, fatty acid.
Serum FA concentrations are means ± standard errors.

Table 5. Veterinary clinical evaluations and overall scores for dogs completing the study according to protocol.

Parameter	Food	Day 0	Day 21	Day 45	Day 90	*P* Versus Food A
Lameness[a]	A	2.20 ± 0.13	2.00 ± 0.12	1.88 ± 0.12	1.79 ± 0.12	
	B	2.16 ± 0.13	1.94 ± 0.11	1.89 ± 0.12	1.83 ± 0.12	.46
	C	2.00 ± 0.12	1.74 ± 0.11	1.71 ± 0.11	1.64 ± 0.11	.04
Weight bearing[a]	A	1.91 ± 0.13	1.70 ± 0.12	1.69 ± 0.12	1.73 ± 0.12	
	B	1.91 ± 0.12	1.70 ± 0.11	1.64 ± 0.11	1.60 ± 0.11	.32
	C	1.68 ± 0.11	1.56 ± 0.11	1.61 ± 0.11	1.40 ± 0.10	.03
Range of motion[a]	A	2.33 ± 0.14	2.03 ± 0.14	1.95 ± 0.13	1.90 ± 0.13	
	B	2.55 ± 0.15	2.30 ± 0.15	2.25 ± 0.14	2.10 ± 0.14	.94
	C	2.47 ± 0.15	2.08 ± 0.14	2.14 ± 0.14	2.01 ± 0.14	.79
Reluctance to hold up contralateral limb[a]	A	1.81 ± 0.13	1.71 ± 0.12	1.58 ± 0.11	1.60 ± 0.12	
	B	1.88 ± 0.13	1.75 ± 0.12	1.70 ± 0.11	1.63 ± 0.11	.73
	C	1.75 ± 0.12	1.54 ± 0.11	1.60 ± 0.11	1.46 ± 0.11	.20
Pain on palpation of affected joint[a]	A	2.19 ± 0.15	1.87 ± 0.14	1.81 ± 0.13	1.75 ± 0.12	
	B	2.27 ± 0.15	2.02 ± 0.14	1.88 ± 0.13	1.78 ± 0.12	.75
	C	2.28 ± 0.15	1.88 ± 0.14	1.85 ± 0.13	1.69 ± 0.12	.54
Progression of arthritis[b]	A	—	—	—	2.32 ± 0.12	
	B	—	—	—	2.16 ± 0.11	.13
	C	—	—	—	1.99 ± 0.11	.0008
Overall arthritic condition[c]	A	—	—	—	3.15 ± 0.17	
	B	—	—	—	2.86 ± 0.15	.07
	C	—	—	—	2.55 ± 0.14	.001

Scores shown are means ± standard error.

[a]1, none; 2, mild; 3, moderate; 4, severe; *P*-values determined by ANOVA.

[b]1, significantly slowed; 2, slightly slowed; 3, no effect; 4, slightly accelerated; 5, significantly accelerated; *P*-value calculated using a 1-sided Dunnett's test to compare foods B and C with food A.

[c]1, extreme improvement; 2, moderate improvement; 3, slight improvement; 4, no change; 5, slight deterioration; 6, moderate deterioration; 7, extreme deterioration; *P*-value calculated using a 1-sided Dunnett's test to compare foods B and C with food A.

medication (data not shown). In addition, there were no significant differences (time × food effect) between dogs on food A and those on food B. However, there was a significant difference for 2 signs, lameness ($P=.03$) and weight bearing ($P=.04$), between dogs on food A and those on food C. With the exception of weight bearing for diet A, ANOVA showed that all signs significantly improved over time for all diets (data not shown). Finally, of the 35 dogs dismissed during the course of the study, 21 had at least 1 orthopedic evaluation. Including these data in the analysis did not affect the results (data not shown).

Overall Changes in Arthritic Condition According to Owners' Input

At the end of the study (day 90), investigators were asked to estimate the progression of clinical signs and overall change in arthritic condition based on their own orthopedic evaluation and the pet owners' input. As with the 5 clinical signs, the effects of the treatments did not significantly vary between the clinics and were not significantly influenced by the presence of concurrent medication (data not shown). Compared with food A, food C produced a significant improvement in both the progression of arthritic condition and the overall change in arthritic condition (Table 5). There were not significant differences between the scores for dogs on foods B and A.

Adverse Events

A total of 16 adverse events were reported during this study. Two of these were considered related to the study foods, including 1 case of mild diarrhea and vomiting for a dog fed food A and 1 case of mild diarrhea for a dog fed food B. Both of these dogs discontinued treatment.

Discussion

Feeding a food supplemented with fish oil[a] improves weight bearing and some clinical signs in dogs with OA.[19,20] Here, we show that further increasing the amount of fish oil in the food leads to modest additional significant improvements in clinical signs of OA as determined by primary care veterinarians. These results support the idea that components of fish oil, most likely the omega-3 FAs EPA and DHA,[14,24] can be beneficial in dogs with OA.

We included only dogs with OA of the hip or stifle to eliminate differences in the evaluation of forelimb and hindlimb lameness and to facilitate detection of changes in joint function. Changes in clinical signs of OA were assessed by investigators using a series of subjective scores because other than force-plate studies, which require specialized equipment,[25] there are currently no validated objective measures for assessing short-term changes in OA in dogs. The scoring system was similar to those used in our previous studies,[19,20] although we added 2 scores for overall changes in clinical signs of OA

between study start and study end. These 2 overall scores were designed to capture both the investigator's ability to discern clinical changes and the owner's ability to observe their pets over extended periods of time in their natural setting. We did not assess radiographic signs of OA during this study because we did not expect to see meaningful changes within the 90-day study period and because previous studies have shown that radiographs do not accurately reflect limb function in dogs.[26]

The 2 experimental foods had approximately 2 and 3 times the amount of fish oil as the baseline food (food A).[a] The amount of flaxseed oil was reduced in the experimental foods to maintain a similar ratio of fat and carbohydrate, although there was a slight increase in total fat content (14.0% for food A, 16.0% for food B, and 20.8% for food C). Chemical analysis showed that the amount of EPA and DHA, 2 major fish oil omega-3 FAs with anti-inflammatory effects,[14,24] were approximately 2-fold higher in food B and 3-fold higher in food C than in food A.

All 3 foods appeared to be generally safe. The only adverse events that might have been related to the study foods were 1 case of mild diarrhea and vomiting for the foods with the 2 lowest omega-3 FA concentrations (foods A and B). Thus, there did not appear to be dose-dependent treatment-related adverse events, and if necessary, it should be possible to safely raise the dietary level of fish oil at least to the concentration provided by food C.

Feeding all 3 foods led to increases in the individual (EPA, DHA, and ALA) and total serum omega-3 FA concentrations over time. Not unexpectedly, there were significant differences between how fast the 2 experimental foods (B and C) and baseline food (food A) altered serum FA concentrations. Furthermore, the serum concentrations of EPA and DHA increased in direct proportion with their concentrations in the foods. With respect to the measured FAs, the largest effect of an increased concentration of dietary fish oil was on EPA, consistent with it being a major omega-3 FA in fish oil.[27] The foods also resulted in significantly higher concentrations of the omega-3 FAs DHA and ALA as well as reduced concentrations of omega-6 FAs including AA. A reduction in AA combined with competitive inhibition of AA conversion to eicosanoids by EPA and DHA is expected to help reduce inflammation by altering the types and amounts of eicosanoids produced.[15] An increase in ALA might also help reduce the severity of OA by altering the eicosanoid and cytokine profile and by decreasing reactive oxygen levels and lymphocyte reactivity.[15]

Compared with food A, the food with an intermediate level of fish oil (food B) did not result in significant differences in individual clinical signs or in the 2 overall scores at study end. However, the food with the highest level of fish oil (food C) resulted in a significant improvement in 2 clinical signs (lameness and weight bearing) as well as in the 2 overall scores. In addition, regression analysis indicated a close relationship between the amount of added fish oil in the 3 foods (as represented by EPA+DHA) and decreases in the 2 overall scores.

Our statistical modeling indicated that heterogeneity between clinics or investigators did not significantly influence the results. In addition, our analysis indicated that the use of concurrent medication did not affect the findings. Finally, there were no differences in the characteristics (sex, reproductive status, primary affected joint, weight, or BCS) of the dogs at baseline (study start) or in their weights or BCS at the end of the study.

The observed improvements in lameness and weight bearing agree with our previous findings from force-plate analysis that dietary supplementation with fish oil can improve weight bearing in dogs with OA.[19] Although the current results are interesting and consistent with our previous findings, the improvements were relatively modest. This was not due to a limitation in the ability to absorb the fish oil FAs, as EPA and DHA concentrations in serum correlated closely with their levels in the food; rather, it might have been due to subjectiveness of the scores combined with relative insensitivity of the scales. We suspect that objective scores would help detect changes in OA severity, but, other than force-plate studies, there are currently no simple validated objective measures for assessing short-term changes in OA in pet dogs.

Footnotes

[a] Prescription Diet Canine j/d, Hill's Pet Nutrition, Topeka, KS
[b] Ocean Nutrition Canada, Dartmouth, NS
[c] SAS version 9.1.3, SAS Institute, Cary, NC

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