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A prospective, randomized, double blind, placebo-controlled evaluation of the effects of eicosapentaenoic acid and docosahexaenoic acid on the clinical signs and erythrocyte membrane polyunsaturated fatty acid concentrations in dogs with osteoarthritis ☆

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ABSTRACT

Background: Osteoarthritis (OA) in dogs is a prevalent and serious condition. The most common treatment for the clinical signs of OA in dogs is the administration of nonsteroidal antiiflammatory pharmaceuticals. Omega-3 ($n-3$) fatty acids have been shown to reduce the clinical signs of osteoarthritis in dogs.
Objective: The primary goals of this study were 1) to determine the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the clinical signs of OA in dogs, 2) to evaluate the effects of supplementation on the arachadonic acid (ARA)/ (EPA+DHA) algorithm and 3) to correlate alterations in the ARA/(EPA+DHA) with changes in the clinical signs of canine OA.
Methods: Seventy-eight client owned dogs were enrolled in a prospective, randomized, double-blind, placebo controlled clinical trial. Dogs were randomized to placebo oil or triglyceride n-3 oil (providing an average dose of 69 mg EPA+DHA/kg/day). Orthopedic examinations and blood analyses were performed at baseline, day 42, and day 84. A single investigator confirmed a diagnosis of OA of the coxofemoral joints and/or stifle joints in all dogs.
Results: Seventy-four dogs completed the trial. All clinical outcomes for measuring discomfort, lameness, and joint severity at day 84 and all blood metrics at day 42 and day 84 significantly ($p < 0.05$) improved compared with placebo. No major side effects were observed.
Conclusion and clinical relevance: This study demonstrated that the daily supplementation of a dogs diet with EPA and DHA shifts the blood fatty acid concentrations correlating to relief of clinical signs associated with OA in dogs.

1. Introduction

OA affects up to 20% of dogs >1 year of age [1]. The disease afflicts dogs of all breeds and ages. Common approaches to the disease include attempts at prevention, slowing progression, and managing the clinical signs associated with OA. These are accomplished with appropriate nutrition, body- weight control, exercise, physical therapy, and anti-inflammatory and analgesic medications [2,3]. Nonsteroidal anti-inflammatory drugs (NSAID) are effective modes of treatment, but have potential negative systemic side effects such as gastrointestinal ulceration, liver and kidney damage, and accelerated cartilage degeneration [3,4]. There is a pressing need for safe alternatives to manage OA. Previous studies in dogs have supported the efficacy of the marine $n-3$ fatty acids in OA [2,3,5,6–8.]

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ALA, α-Linolenic acid; ARA, arachidonic acid; EM, erythrocyte membrane, $n-3$ omega-3 fatty acids, $n-6$ omega-6 fatty acids; OA, osteoarthritis; iFATS, inflammatory fatty acid target score

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The primary $n-3$ fatty acids are EPA (eicosapentaenoic acid, C20:5$n-3$), DHA (docosahexaenoic acid, C22:6$n-3$), and ALA (alpha-linolenic acid, C18:3$n-3$). Both EPA and DHA are found in high concentrations in fish oils. Both EPA and DHA have potent anti-inflammatory properties, and DHA is a major component of the central nervous system. ALA is found in some seed oils (e.g., flaxseed oil) and requires the enzymes delta-6 and delta-5 desaturases to convert it into EPA and DHA in the body [5,7–11]. Dogs have a limited ability to accomplish this conversion [5,9,10,12], therefore providing preformed EPA and DHA is the most efficient way to increase tissue concentrations of these fatty acids. The other family of essential fatty acids are the $n-6$ fatty acids including LA (linoleic acid, C18:2$n-6$), GLA (gamma-linolenic acid, C18:3$n-6$), and ARA (arachidonic acid, C20:4$n-6$). The former two, especially LA, are found primarily in vegetable oils and food products made with them. ARA is metabolized through multiple pathways (cyclooxygenase, lipoxygenase, cytochrome P450 monooxygenases, etc.), and some of its metabolites are inflammatory mediators [13]. EPA and/or DHA, can be utilized to decrease the amount of ARA available as a substrate for inflammatory eicosanoid production. The body needs episodic inflammation to heal wounds and fight infection, but chronic inflammation can lead to chronic disease.

Consuming fish oils results in the partial replacement of ARA in cell membranes by EPA and DHA. This leads to decreased availability of ARA for conversion into leukotrienes and prostaglandins [14,15]. EPA and DHA give rise to lesser inflammatory molecules (e.g., prostaglandin E3, leukotriene B5) with a resultant competitive inhibition of ARA metabolism [11]. The net effect is a reduction in the anti-inflammatory environment systemically and within the joint.

The primary goals of this study were (1) to determine the effects of daily supplementation of a natural triglyceride form of EPA and DHA (in a ratio of 3:2; Canine Omega Benefits, Veterinarian Recommended Solutions, Plymouth Meeting, PA) on the clinical signs of OA in dogs, (2) to evaluate the effects of supplementation on the blood ARA/EPA+DHA ratio (Inflammatory Fatty Acid target Score, iFATS™), and (3) to correlate changes in the iFATS with changes in OA clinical signs.

2. Materials and methods

2.1. Design

This was a prospective, randomized, double blind, placebo controlled study. Any dog greater than 2 years of age with naturally occurring OA of the stifle or coxofemoral joint as previously diagnosed by a veterinarian physical examination and radiographs was eligible to participate. Exclusion criteria included any dog with a disease in which surgery was recommended (cruciate ligament instability, grade two medial or lateral patella luxation, hip luxation or significant subluxation), concurrent active neurologic conditions, any comorbidity causing weakness or discomfort in the limbs not directly related to osteoarthritis, or current administration of an $n-3$ supplement or diet supplemented with $n-3$. Patients previously taking NSAIDs were enrolled if the pet owner refrained from administering the NSAID for two weeks or more before enrollment. If dogs required rescue analgesia during the trial, they were removed from the study and referred to their primary veterinarian. The data from these dogs was not included in the final analysis. Dogs were recruited from and evaluated at four primary care practices[1]. All pet owners were educated on the study, the product and placebo, and each owner signed a consent form prior to enrolment. All examinations, blood work, and product were administered at no cost to the owner. All animals in this study were the property of a responsible adult pet owner that consciously consented to the participation of their pet in the study. No Animal Use Committee was consulted with for the study; however, a standardized pet owner consent and acknowledgment form was described to and read and signed by every pet owner and each medical director of the participating clinic read and acknowledged the study protocol prior to initiating the trial. All physical examinations and blood collections were performed in a routine manner and in the presence of the pet owner. The ARRIVE guidelines were complied with during the entire clinical trial.

2.2. Interventions

The active treatment group received the $n-3$ product and the placebo group received a medical grade mineral oil. The $n-3$ product contained EPA and DHA, derived from a mixture of anchovy, sardine, and mackerel, in a ratio of 3:2 in a natural triglyceride form. Both oils were distributed in 500 mL, tinted glass bottles with a pump that delivers 3 mL per pump. The label on the outside of the bottle contained a randomized study number, assigned by the study statistician, who also maintained all blinding, held the key for randomization, and performed all data analysis. No block randomization was performed. The number of pumps to deliver to the patient's food dish per day was based on body weight and written on the bottle label. The pet owner was instructed to administer the daily dose once per day either with the morning or evening feeding but that the frequency and time of dosing was consistent throughout the study period. Each mL of the $n-3$ product contained 240 mg of combined EPA and DHA. Dosing schedules for the study were as recommended by the manufacturer: 1 pump (720 mg EPA and DHA) for dogs weighing 4.5–13.6 kg, 2 pumps (1440 mg of EPA and DHA) for 13.7–27.2 kg; 3 pumps (2160 mg of EPA and DHA) for 27.3–40.8 kg, and 4 pumps (2880 mg of EPA and DHA) for dogs weighing greater than 40.8 kg.

2.3. Assessments

Compliance was assessed by having an independent study technician weigh each bottle at day 42 and day 84 and compare that information to the amount of doses recommended to be administered per day.

A single investigator (SJM) blinded to treatment assignment conducted all clinical examinations. Radiography and physical examination were used to confirm a diagnosis of OA. Evaluations by the investigator included a physical examination, a lameness/discomfort visual analogue scale (VAS), a lameness/discomfort severity grade, and an individual and total joint score; and at day 42 and 84 an investigator improvement VAS.

The Lameness/Discomfort VAS is a 10 cm scale on the vertical axis. At the bottom is a description of a normal dog and at the top of the scale is a description of a dog debilitated by OA. A horizontal line is drawn on the scale that best describes the pet on that day. A ruler is used to measure from baseline to the horizontal line and is recorded in centimeters.

The Lameness Grade is derived from a series of numbers (0–10) spaced evenly across the top of the evaluation form. The investigator circles the number that best describes the pet on that day. Zero represents a normal dog and 10 represents a dog debilitated by OA.

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