

Canine Omega-3 Research Studies Summary

Canine research studies that support the beneficial effects of omega-3.

Omega-3 supplementation is beneficial to maintain:

- Joint health
- Heart health and endurance
- Growth and reproduction
- Renal function
- Immune system health
- Skin and coat health

Joint health

- Hall JA, Henry LR, Jha S, Skinner MM, Jewell DE, Wander RC. Dietary (n-3) fatty acids alter plasma fatty acids and leukotriene B synthesis by stimulated neutrophils from healthy geriatric Beagles. *Prostaglandins Leukot Essent Fatty Acids*. 2005 Nov;73(5):335-41.

The study objective was to determine the effect of feeding food enriched in omega-3 (n-3) fatty acids (FA) on plasma FA profiles and leukotriene B (LTB) synthesis by stimulated peripheral blood neutrophils from dogs. For 36 weeks, two groups of dogs (n = 5) were fed food that contained either a low ratio of omega-6 to omega-3 FA (1.31:1; fish oil-enriched food) or a high ratio of omega-6 to omega-3 FA (40.6:1; corn oil-enriched food).

Consumption of food enriched in fish oil resulted in higher plasma concentrations of eicosapentaenoic acid and docosahexaenoic acid and lower concentrations of arachidonic acid. Neutrophils from dogs fed fish oil-enriched food produced 7.6-fold more LTB(5) (P = 0.002), and the ratio of LTB(5)-LTB(4) concentrations was 8.3-fold higher (P < 0.001) compared with dogs fed corn oil-enriched food. Dietary FA can modulate leukotriene production by neutrophils in dogs, and suggests that foods enriched in omega-3 (n-3) FA from fish oil may have value in the treatment of canine inflammatory diseases.

- Hansen RA, Harris MA, Pluhar GE, Motta T, Brevard S, Ogilvie GK, Fettman MJ, Allen KG. Fish oil decreases matrix metalloproteinases in knee synovia of dogs with inflammatory joint disease. *J Nutr Biochem*. 2007 May 23.

This study was designed to determine whether dietary fish oil affects the expression and activity of matrix metalloproteinases (MMP), tissue inhibitors of MMP-2 (TIMP-2) and urokinase plasminogen activator (uPA) in synovial fluid from dogs with spontaneously occurring stifle (knee) instability in a single hind limb resulting from acute cranial cruciate ligament (CCL) injury. Two groups of 12 dogs were fed diets from 1 week prior to surgery on the affected knee to 56 days post-surgery. The fish oil and control diets provided 90 and 4.5 mg, respectively, of combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)/kg body weight per day. Plasma and synovial fluid, from both surgical and nonsurgical knee joints, were obtained at start of the diet (-7), surgery day (0) and 7, 14, 28 and 56 days post-surgery.

Plasma total EPA and DHA were significantly increased, and plasma total arachidonic acid (AA) was significantly decreased by the fish oil diet. In synovial fluid from the nonsurgical knee, fish oil treatment significantly decreased proMMP-2 expression at Days 7 and 14, and proMMP-9 expression at Day 56, and uPA activity at 28 days and significantly increased TIMP-2 expression at Days 7 and 28. There were no differences in MMP expression or activity, TIMP-2 expression and uPA activity in the surgical joint synovial fluid at any time throughout the study. These results suggest that dietary fish oil may exert beneficial effects on synovial fluid MMP and TIMP-2 equilibrium in the uninjured stifle of dogs with unilateral CCL injury.

Heart health and endurance

- Freeman LM, Rush JE, Markwell PJ. Effects of dietary modification in dogs with early chronic valvular disease. *J Vet Intern Med*. 2006 Sep-Oct;20(5):1116-26.

BACKGROUND: The potential benefits of nutritional modification in early canine cardiac disease are not known. HYPOTHESIS: We hypothesized that echocardiographic, neuroendocrine, and nutritional variables will differ between dogs with asymptomatic chronic valvular disease (CVD) and healthy controls, and that a moderately reduced sodium diet enriched with antioxidants, omega-3 (n-3) fatty acids, taurine, carnitine, and arginine will alter these variables in dogs with CVD. METHODS: Echocardiography was performed and blood was collected. After baseline comparison with healthy controls, all dogs with CVD were fed a low-sodium

run-in diet for 4 weeks, reevaluated, and then randomized to receive either the cardiac diet or a placebo diet for 4 weeks.

RESULTS: At baseline, dogs with CVD (n = 29) had significantly lower circulating sodium, chloride, arginine, and methionine concentrations and higher plasma concentrations of atrial natriuretic peptide compared to healthy controls. In dogs with CVD, plasma aldosterone concentration and heart rate increased significantly after 4 weeks of eating the run-in diet. The cardiac diet group (n = 14) had larger increases in levels of cholesterol (P = .001), triglycerides (P = .02), eicosapentaenoic acid (P < .001), docosahexaenoic acid (P < .001), total omega-3 fatty acids (P < .001), vitamin C (P = 0.04), alpha-tocopherol (P < .001), and gamma-tocopherol (P < .001) compared to the placebo diet group (n = 15). The cardiac diet group also had larger reductions in maximal left-atrial dimension (P = .003), left-ventricular internal dimension in diastole (P = .03), and weight-based maximal left-atrial dimension (P = .03). **CONCLUSIONS AND CLINICAL IMPORTANCE:** Observed changes in both blood variables and echocardiographic measurements warrant additional studies on dietary modifications in dogs with early CVD.

- Smith CE, Freeman LM, Rush JE, Cunningham SM, Biourge V. Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med.* 2007 Mar-Apr; 21(2):265-73.

BACKGROUND: Omega-3 fatty acids have been shown to reduce arrhythmia in animal models and people. These effects have not been studied in dogs with spontaneously occurring arrhythmia. **HYPOTHESIS:** Fish oil will reduce the frequency of ventricular arrhythmia in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy (ARVC). **ANIMALS:** Twenty-four Boxers with ARVC were included in this study. **METHODS:** Asymptomatic Boxers not receiving antiarrhythmic medications were evaluated with echocardiogram and electrocardiogram. Dogs with at least 1 ventricular premature contraction (VPC) received 24-hour ambulatory electrocardiography (AECG) recordings. Dogs with > 95 VPCs in 24 hours were randomized to 1 of 3 treatments: (1) Fish oil, 2 g; (2) Flax oil, 2 g; or (3) sunflower oil, 2 g (Control group), for 6 weeks. Investigators and owners were blinded to the treatment groups. All baseline measurements were repeated after the 6-week supplementation.

RESULTS: There were no differences at baseline for age, sex, blood pressure, weight, echocardiographic measurements, or VPCs. Median number of VPCs in 24 hours for all dogs was 543 (range, 96-40,063) at baseline and 193 (range, 6-14,825) after 6 weeks of supplementation. VPCs/24 h were reduced for the Fish oil group (baseline median = 397 [range, 249-10,587]; 6-week median = 162 [range, 16-3,781]; P = .02), but not for the Flax oil (P = .58) or Control (P = .48) groups.

CONCLUSIONS AND CLINICAL IMPORTANCE: These data suggest that fish oil, but not flax oil, supplementation for 6 weeks reduces arrhythmia in Boxers with ARVC and that it could be useful in treating this common disease. Further studies are needed to determine optimal dose and duration of treatment.

- Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation.* 1999 May 11;99(18):2452-7.

BACKGROUND: Rat diets high in fish oil have been shown to be protective against ischemia-induced fatal ventricular arrhythmias. Increasing evidence suggests that this may also apply to humans. To confirm the evidence in animals, we tested a concentrate of the free fish-oil fatty acids and found them to be antiarrhythmic. In this study, we tested the pure free fatty acids of the 2 major dietary omega-3 polyunsaturated fatty acids in fish oil: cis-5,8,11,14, 17-eicosapentaenoic acid (C20:5omega-3) and cis-4,7,10,13,16, 19-docosahexaenoic acid (C22:6omega-3), and the parent omega-3 fatty acid in some vegetable oils, cis-9,12,15-alpha-linolenic acid (C18:3omega-3), administered intravenously on albumin or a phospholipid emulsion.

METHODS AND RESULTS: The tests were performed in a dog model of cardiac sudden death. Dogs were prepared with a large anterior wall myocardial infarction produced surgically and an inflatable cuff placed around the left circumflex coronary artery. With the dogs running on a treadmill 1 month after the surgery, occlusion of the left circumflex artery regularly produced ventricular fibrillation in the control tests done 1 week before and after the test, with the omega-3 fatty acids administered intravenously as their pure free fatty acid. With infusion of the eicosapentaenoic acid, 5 of 7 dogs were protected from fatal ventricular arrhythmias (P<0.02). With docosahexaenoic acid, 6 of 8 dogs were protected, and with alpha-linolenic acid, 6 of 8 dogs were also protected (P<0.004 for each). The before and after control studies performed on the same animal all resulted in fatal ventricular arrhythmias, from which they were defibrillated.

CONCLUSIONS: These results indicate that purified omega-3 fatty acids can prevent ischemia-induced ventricular fibrillation in this dog model of sudden cardiac death.

Renal function

- Brown SA, Brown CA, Crowell WA, Barsanti JA, Kang CW, Allen T, Cowell C, Finco DR. Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. *J Lab Clin Med.* 2000 Mar;135(3):275-86.

Dietary supplementation with polyunsaturated fatty acids (PUFAs) alters the course of experimental kidney disease in dogs. In particular, supplementation with omega-6 PUFAs hastens the decline of kidney function, and omega-3 PUFAs are renoprotective. We investigated the early stages of renal insufficiency to determine whether PUFA supplementation altered the magnitude of hypercholesterolemia or glomerular hemodynamics. Two months after 11/12 nephrectomy, dogs were randomly divided into three groups of 6 animals each. Each group of dogs was then fed a low-fat basal diet supplemented with one of three sources of lipid to achieve a final concentration of 15% added fat. Fat sources were rich in omega-3 PUFAs (menhaden fish oil, group FO), omega-6 PUFAs (safflower oil, group SO), or saturated fatty acids (beef tallow, group C).

Early in renal insufficiency, before significant kidney damage, group FO had a lower ($P < .05$) serum cholesterol concentration and tended to have a lower urinary prostaglandin E2 (PGE2) and thromboxane A2 (TxA2) excretion than group C. In contrast, group SO had a higher mean glomerular capillary pressure ($P < .05$) and more glomerular enlargement ($P < .05$) and tended to have higher eicosanoid excretion rates than group C. These differences in lipid metabolism, glomerular hypertension and hypertrophy, and urinary eicosanoid metabolism could explain, in part, the beneficial effects of omega-3 PUFAs and the detrimental effects of omega-6 PUFAs when administered on a long-term basis in this model of renal insufficiency.

- Brown SA, Finco DR, Brown CA. Is there a role for dietary polyunsaturated fatty acid supplementation in canine renal disease? *J Nutr.* 1998 Dec;128(12 Suppl):2765S-2767S.

Dogs with spontaneous renal diseases frequently develop progressive uremia. After partial nephrectomy, a similar pattern of progressively declining renal function develops. This pattern may be attributed in part to the development of glomerular hypertension in remnant canine nephrons. Changes in the composition of dietary polyunsaturated fatty acids (PUFA) modify glomerular hemodynamics in normal rats and affect the chronic course of renal disease in partially nephrectomized rats. Thus, dietary PUFA supplementation might alter progressive canine nephropathies. However, the response of dogs with renal insufficiency to dietary manipulations frequently differs substantially from that of laboratory rodents, and the effects of dietary PUFA composition have been poorly characterized in dogs with chronic renal disease.

Here we address the hypothesis that dietary PUFA supplementation may delay the progression of chronic renal insufficiency in dogs. In particular, dogs ingesting diets supplemented with (n-6) PUFA exhibited severe glomerular hypertension associated with rapidly progressive renal failure. In contrast, dietary supplementation with (n-3) PUFA prevented deterioration of the glomerular filtration rate and preserved renal structure. The results of these model studies demonstrate that dietary PUFA supplementation may alter renal hemodynamics and the long-term course of renal injury in dogs. Clinical trials to address the potential benefits of dietary (n-3) PUFA supplementation in a variety of spontaneous renal diseases seem warranted.

Growth and reproduction

- Heinemann KM, Bauer JE. Docosahexaenoic acid and neurologic development in animals. *J Am Vet Med Assoc.* 2006 Mar 1;228(5):700-5, 655.

Feeding dams a diet enriched with DHA during gestation and lactation has been associated with improvements in neurologic development of their puppies. Also, feeding diets or supplements containing DHA may improve memory or learning in young dogs.

- Heinemann KM, Waldron MK, Bigley KE, Lees GE, Bauer JE. Long-chain (n-3) polyunsaturated fatty acids are more efficient than alpha-linolenic acid in improving electroretinogram responses of puppies exposed during gestation, lactation, and weaning. *J Nutr.* 2005 Aug;135(8):1960-6.

Long-chain PUFAs (LCPUFAs) are essential for proper neural and retinal development in many mammalian species. We investigated puppies born to dogs fed diets containing varying amounts of vegetable and marine (n-3) fatty acids during gestation/lactation. The fatty acid compositions of dogs' milk and puppy plasma phospholipids were evaluated, and electroretinographic responses of the young dogs were determined after they were weaned to the same diets. Dogs' milk fatty acid composition reflected the diets fed during gestation/lactation. The milk of dogs fed a high alpha-linolenic acid (ALA) diet was enriched in ALA but not docosahexaenoic acid (DHA). Puppies fed this ALA-enriched milk accumulated more plasma

phospholipid DHA than the low (n-3) fatty acid group. However, this accumulation was less than that obtained in puppies fed preformed DHA during development and suckling ($P < 0.05$).

Electroretinograms (ERGs) of 12-wk-old puppies revealed significantly improved visual performance in dogs fed the highest amounts of omega-3 (n-3) LCPUFAs ($P < 0.05$). These puppies demonstrated improved rod response (improved amplitude and implicit time of the a-wave, $P < 0.05$). Puppies from the low (n-3) fatty acid group exhibited the poorest ERG responses compared with the high-marine or high-vegetable (n-3) groups. A novel parameter devised in this study, the initial intensity at which the a-wave was detectable (i.e., threshold intensity), also demonstrated that retinal response of puppies consuming the (n-3) LCPUFA-containing diets occurred at lower light intensity, thereby exhibiting greater rod sensitivity, than the other diet groups. These findings indicate that preformed dietary (n-3) LCPUFA is more effective than ALA in enriching plasma DHA during perinatal development and results in improved visual performance in developing dogs.

Immune system health

- Kearns RJ, Hayek MG, Turek JJ, Meydani M, Burr JR, Greene RJ, Marshall CA, Adams SM, Borgert RC, Reinhart GA. Effect of age, breed and dietary omega-6 (n-6): omega-3 (n-3) fatty acid ratio on immune function, eicosanoid production, and lipid peroxidation in young and aged dogs. *Vet Immunol Immunopathol.* 1999 Aug 2;69(2-4):165-83.

The focus of this study was to examine the influence of age and diet on various parameters of immune function in young and old Fox Terriers and Labrador Retrievers. Eighteen young and old dogs were utilized for this study. Young and old dogs were fed a basal diet containing an (n-6):(n-3) ratio of 25:1 for sixty days (Phase I). Half of the dogs were then switched to a diet with an (n-6):(n-3) ratio of 5:1, and all were maintained on their respective diets for an additional sixty days (Phase II).

Results from these studies revealed an age-associated decline in several immune parameters measured. Both these breeds demonstrated a reduction in sheep red blood cell titers, as well as in their ability to respond to different mitogens. Interestingly, this decline was greater in Fox Terriers, suggesting a decrease in cellular proliferative capacity in lymphocytes isolated from the larger breed. Neither cytokine production or DTH response was affected by age. Diet and breed interactions resulted in a significant increase in T- and B-cell mitogen responsiveness. In contrast, supplementation with n-3 fatty acids did not affect IL-1, IL-6 or TNF-alpha production.

Supplementation with n-3 fatty acids resulted in increased PGE3 production from peritoneal macrophages but had no effect on PGE2 production from peripheral blood mononuclear cells or peritoneal macrophages. The n-3 fatty acid supplementation did not influence alpha-tocopherol status although older dogs had significantly lower serum alpha-tocopherol concentrations. Oxidative status of these dogs was assessed by serum levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Feeding an n-3-enriched diet did not affect 4-HNE levels but significantly decreased MDA levels in old dogs. In summary, this study indicates that feeding a diet containing an (n-6):(n-3) fatty acid ratio of 5:1 had a positive, rather than a negative, effect on the immune response of young or geriatric dogs.

- Wander RC, Hall JA, Gradin JL, Du S-H, Jewell DE. The ratio of dietary (n-6) to (n-3) fatty acids influences immune system function, eicosanoid metabolism, lipid peroxidation and vitamin E status in aged dogs. *J Nutr* 1997;127:1198-1205.

- Mooney MA, Vaughn DM, Reinhart GA, Powers RD, Wright JC, Hoffman CE, Swaim SF, Baker HJ. Evaluation of the effects of n-3 fatty acid-containing diets on the inflammatory stage of wound healing in dogs. *Am J Vet Res* 1998; 59:859-863.

- Filburn CR, Griffin D. Canine plasma and erythrocyte response to a docosahexaenoic acid-enriched supplement: characterization and potential benefits. *Vet Ther.* 2005 Spring;6(1):29-42.

Results of this study confirm that dietary supplementation in dogs with a natural source of omega-3 fatty acids (salmon oil), with a docosahexaenoic acid:eicosapentaenoic acid (DHA:EPA) ratio of 1.5:1, increases plasma and red blood cell levels of these fatty acids. Supplementation with this DHA-enriched oil improves the long-chain polyunsaturated fatty acid omega-6:omega-3 (n-6:n-3) ratio, which may benefit dogs of all ages. Studies describing some of the neurologic, renal, cardiovascular, immune, and musculoskeletal effects of elevated blood levels of n-3 fatty acids, especially DHA, are reviewed. The importance of providing an enriched source of DHA, instead of its shorter precursors, is emphasized.

Skin and coat health

• Mooney MA, Vaughn DM, Reinhart GA, Powers RD, Wright JC, Hoffman CE, Swaim SF, Baker HJ. Evaluation of the effects of omega-3 fatty acid-containing diets on the inflammatory stage of wound healing in dogs. *Am J Vet Res.* 1998 Jul;59(7):859-63.

OBJECTIVES: To ascertain the effects of dietary omega-3 (n-3) fatty acids on biochemical and histopathologic components of the inflammatory stage of wound healing. ANIMALS: 30 purpose-bred Beagles. PROCEDURE: Dogs were allotted to 5 groups of 6. Each group was fed a unique dietary fatty acid ratio of omega-6 to n-3: diet A, 5.3:1; diet B, 10.4:1; diet C, 24.1:1; diet D, 51.6:1; and diet E, 95.8:1. Dogs were fed once daily for 12 weeks, then biopsy specimens were taken from 4-day-old wounds of each dog and analyzed by gas chromatography-mass spectrometry for: prostaglandin E2 (PGE2) metabolites, and ratios of omega-6 to n-3 fatty acids, arachidonic acid (AA) to eicosapentaenoic acid (EPA), adrenic acid to docosahexaenoic acid, and PGE2 to prostaglandin E3 (PGE3) metabolites.

RESULTS: Qualitative analysis was carried out on AA, EPA, adrenic acid, docosahexaenoic acid, and the major metabolite from the PGE2 and PGE3 pathway. These molecules were further quantified with respect to diet to determine significant differences. By analysis of the AA-to-EPA ratio, diet A was different from diets D and E and diets B and C were different from diet E ($P < 0.05$). By analysis of the PGE2-to-PGE3 metabolite ratio, diet A was different from diet E ($P < 0.05$). Though biochemical analysis indicated dietary dependence, histopathologic data indicated no significant difference with respect to diet groups.

CONCLUSION: The biochemical component of the inflammatory stage of wound healing can be manipulated by diet. CLINICAL RELEVANCE: Omega-3 fatty acid-enriched diets can be used to control inflammation associated with dermatologic conditions.

• Harvey RG. A blinded, placebo-controlled study of the efficacy of borage seed oil and fish oil in the management of canine atopy. *Vet Rec.* 1999 Apr 10;144(15):405-7.

Twenty-one dogs with atopy were entered into a blinded, placebo-controlled study lasting eight weeks. They were randomly divided into three groups and were all given supplementary oils orally once daily. The dogs in groups A and B were given borage seed oil and fish oil in combination to provide 176 mg/kg or 88 mg/kg borage seed oil respectively. The dogs in group C were given 204 mg/kg olive oil as a placebo. They were all re-examined after four and eight weeks and scored for pruritus, erythema, oedema, alopecia and self-excoriation.

After eight weeks the scores for erythema and self-excoriation, and the total score for the dogs in group A, and the total score for the dogs in group B were significantly reduced ($P < 0.05$). The dogs in group C showed no significant improvement.

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"It is very important to maintain a balance between omega-3 and omega-6 fatty acids in the diet. An inappropriate balance of these essential fatty acids contributes to the development of disease while a proper balance helps maintain and even improve health. Many researchers believe an imbalance is a significant factor in the rising rate of inflammatory disorders in the United States."

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