

Potential Adverse Effects of Omega-3 Fatty Acids in Dogs and Cats

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Fish oil omega-3 fatty acids, mainly eicosapentaenoic acid and docosahexaenoic acid, are used in the management of several diseases in companion animal medicine, many of which are inflammatory in nature. This review describes metabolic differences among omega-3 fatty acids and outlines potential adverse effects that may occur with their supplementation in dogs and cats with a special focus on omega-3 fatty acids from fish oil. Important potential adverse effects of omega-3 fatty acid supplementation include altered platelet function, gastrointestinal adverse effects, detrimental effects on wound healing, lipid peroxidation, potential for nutrient excess and toxin exposure, weight gain, altered immune function, effects on glycemic control and insulin sensitivity, and nutrient-drug interactions.

Key words: Dietary fat; Dietary supplements; Nutraceuticals; Nutrition.

Fish oil omega-3 fatty acids have been investigated for benefits in management of several diseases and often are recommended for management of clinical problems including neoplasia,¹ dermatologic disease,^{2–4} hyperlipidemia,^{5,6} cardiovascular disease,^{7,8} renal disease,^{9,10} gastrointestinal disease,^{11,12} and orthopedic disease.^{13–16} Because omega-3 fatty acids are nutrients used in the management of disease, they are considered nutraceuticals. The term nutraceutical refers to a nutrient that has characteristics of a drug.¹⁷ Omega-3 fatty acids, however, are different from drugs because relatively high doses of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are required for the treatment of disease as compared to most drugs, because most commercial pet foods contain a source of omega-3 fatty acids, and because DHA and possibly EPA are required nutrients for some lifestages (especially during growth and development). Like all drugs and dietary supplements, there is potential for adverse effects with usage of omega-3 fatty acids, especially when diets are supplemented with them or when they are present in diets in large amounts.

Currently, there are few commercial pet foods with EPA and DHA concentrations adequate for treatment of disease. Joint diets, renal diets, and diets for dermatologic conditions typically contain more omega-3 fatty acids than maintenance diets, but even therapeutic diets may not supply enough omega-3 fatty acids for treatment of disease. Target ranges for EPA and DHA vary quite widely for different conditions, but typically fall between 50 and 220 mg/kg body weight. The higher dosages often are used to lower serum triglyceride concentrations in patients

Abbreviations:

AA	arachidonic acid
ALA	alpha-linolenic acid
DHA	docosahexaenoic acid
DTH	delayed-type hypersensitivity
EPA	eicosapentaenoic acid
LA	linoleic acid
n-6:n-3	dietary omega-6 to omega-3 ratio
PUFA(s)	polyunsaturated fatty acid(s)

with hypertriglyceridemia, whereas lower dosages are more commonly used for inflammatory conditions, renal disease, and cardiac disease. Commercial diets containing omega-3 fatty acids typically provide less EPA and DHA than desirable and may be advertised as containing omega-3 fatty acids but contain flaxseed or canola oil (rich in alpha-linolenic acid [ALA]) instead of fish oil. A discussion of the benefits of EPA and DHA as compared to ALA is included in this review. Because of the lower concentrations of EPA and DHA as compared with other omega-3 fatty acids and target concentrations, the authors frequently recommend supplementing EPA and DHA in addition to using a diet containing omega-3 fatty acids.

The purpose of this review is to outline a number of potential adverse effects associated with use of omega-3 fatty acids, with special focus on adverse effects of EPA and DHA supplementation. This topic was reviewed by Hall in 1996,¹⁸ but the increase in research in the area in both humans and animals, the increase in clinical recommendations for omega-3 fatty acid supplementation, and the increase in commercial pet foods containing EPA and DHA make the topic important to revisit. First, basic concepts of fatty acid metabolism are discussed. Potential adverse effects that are discussed include altered platelet function, gastrointestinal adverse effects, detrimental effects on wound healing, lipid peroxidation, potential for nutrient excess and toxin exposure, weight gain, altered immune function, effects on glycemic control and insulin sensitivity, and nutrient-drug interactions. These adverse effects are summarized in both general and specific manners in Table 1.

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Table 1. Summary of general and specific abnormalities or adverse effects noted with usage of omega-3 fatty acids in dogs and cats.

General Abnormality or Adverse Effect	Specific Abnormality or Adverse Effect	Implicated Fatty Acid Types and Doses ^a
Altered platelet function	Decreased platelet aggregation (cats)	n-6:n-3 = 1.3:1 (no specific dosage of fatty acids mentioned) ³⁸
GI adverse effects	Vomiting, diarrhea, pancreatitis	EPA + DHA 0.79 and 1.98 mg/100 kcal ¹³
Altered wound healing	Decreased epithelialization of wounds after five days (dogs)	n-6:n-3 = 0.3:1 (EPA and DHA from fish oil) ⁵⁵
Lipid peroxidation	Increased plasma and urine thiobarbituric reactive substances (dogs)	n-6:n-3 = 5.4:1 (ALA = 0.7 g/kg diet, EPA = 1.05 g/kg, and DHA = 0.95 g/kg) n-6:n-3 = 1.4:1 (ALA = 0.85 g/kg diet, EPA = 3.0 g/kg, and DHA = 2.65 g/kg) ⁵⁷
	Decreased plasma vitamin E concentration (dogs)	n-6:n-3 = 1.4:1 (ALA, EPA, and DHA same as above) ⁵⁷
Nutrient excess, toxin exposure, or both	Consumption of heavy metals Consumption of chemicals such as polychlorinated biphenyls Hypervitaminosis A and D	No clinical reports in cats or dogs. Development of clinical signs would be product and batch dependent.
Weight gain	Obesity, weight gain, or failure to induce weight loss	No clinical reports in cats or dogs. 1 teaspoon of oil = 40–45 kcal ⁶⁷
Altered immune function	Decreased skin and neutrophil leukotriene B ₄ / increased leukotriene B ₅ (dogs) Decreased neutrophil leukotriene B ₄ / increased leukotriene B ₅ (dogs) Lower delayed-type hypersensitivity response (dogs)	n-6:n-3 = 10:1 and 5:1 (blend of menhaden fish oil and flaxseed) ⁶⁹ ALA = 0.23 g/100 g diet, EPA = 3.07 g/100 g, DHA = 1.00 g/100 g versus ALA = 10.30 g/100 g diet and EPA and DHA not detected ³⁵ n-6:n-3 = 1.4:1 (ALA = 0.85 g/kg diet, EPA = 3.0 g/kg, and DHA = 2.65 g/kg) ⁵⁷ ; n-6:n-3 = 1.4:1 (ALA = 0.5–0.6 g/kg diet, EPA = 1.9 g/kg, DHA = 2.2–2.5 g/kg) ⁷⁰ n-6:n-3 = 1.4:1 (low ALA/high EPA and DHA) ⁷¹
	Decreased CD4 ⁺ T lymphocyte count (dogs)	EPA 1.75 g/kg diet, DHA 2.2 g/kg diet ⁵⁸
	Decreased lymphocyte proliferation (dogs)	
	Higher skin leukotriene B ₅ (cats)	n-6:n-3 = 5:1 (fish oil not flaxseed oil) ⁷³
	Decreased response to histamine (cats)	n-6:n-3 = 5:1 (fish oil and flaxseed oil) ⁷³
Effects on glycemic control and insulin sensitivity	Improved glucose control and decreased serum insulin concentration [cats]	EPA = 3.91% of fatty acids in diet and DHA = 4.72% versus EPA = 0.37% and DHA = 0.46% ⁷⁷
Nutrient-drug interactions	Dependent on the drug and dosage	No clinical reports in cats or dogs

^aDoses reported in the same manner as the reference cited.

Basic Concepts of Fatty Acid Metabolism

Dietary fatty acids can be classified as saturated (containing no double bonds), monounsaturated (containing 1 double bond), or polyunsaturated (containing ≥ 2 double bonds). Polyunsaturated fatty acids (PUFAs) can be classified further as omega-6 or omega-3 depending on the location of the 1st double bond from the methyl (omega) end of the molecule. Fatty acids frequently are described using a shorthand notation based on the number of carbons in the fatty acid chain, the number of double bonds in the fatty acid, and whether the fatty acid is omega-6 or omega-3, if applicable. For example, linoleic acid (LA) contains 18 carbons and 2 double bonds with the 1st double bond occurring after the 6th carbon atom from the methyl end of the structure and designated as 18:2n-6.

Fish oil omega-3 fatty acids are long-chain PUFAs and include EPA (20:5n-3) and DHA (22:6n-3). These fatty acids are characterized by 5 or 6 double bonds with the 1st one occurring between the 3rd and 4th carbon from the methyl end of the fatty acid chain. Theoretically, EPA and DHA can be derived from another omega-3 fatty acid, ALA (18:3n-3). ALA is found in plant products such as flaxseed oil and can be converted to EPA and DHA by desaturation (addition of double bonds to the fatty acid chain) and elongation (addition of an even number of carbons to the fatty acid chain). However, in mammals, ALA is not efficiently converted to EPA and DHA. The conversion rate of ALA to EPA and DHA is believed to be <10% in humans,^{19,20} and also is believed to be rather limited in dogs^{21,22} and cats.^{23,24} Therefore, when supplementing omega-3 fatty acids, fish oil is a more potent and efficient source of EPA and DHA as

compared with products rich in ALA such as flaxseed, linseed, or canola oil. Supplementation of ALA does have benefits, especially in management of dermatologic disease,² but different omega-3 fatty acids have different effects on the body and on disease.

Fish oil omega-3 fatty acids are used for management of the aforementioned diseases primarily because of their anti-inflammatory properties. However, inflammation does not play a major role in the pathogenesis of all of these disorders (eg, some cardiovascular diseases, hyperlipidemia). In these instances, omega-3 fatty acids are believed to have beneficial effects in addition to their role in decreasing inflammation. For example, omega-3 fatty acids are thought to have antitumor effects¹ and effects on blood lipid concentrations,^{5,6,25} and improved receptor and ion channel functions.^{26,27}

Omega-6 fatty acids have a double bond between the 6th and 7th carbon from the omega-end of the fatty acid molecule. One of the omega-6 fatty acids is LA, which is considered essential in all mammals because of lack of the enzyme needed for its synthesis.^{24,28} Linoleic acid is efficiently converted to arachidonic acid (AA, 20:4n-6) in dogs, but not in cats. Delta-6 desaturase regulates the 1st step in the desaturation of essential fatty acids; it adds a double bond between the 6th and 7th carbons from the carboxyl end of the fatty acid.²⁹ Cats have a dietary requirement for AA because of limited delta-6 desaturase activity.²³

Lipid metabolites, also called eicosanoids, are derived from long-chain PUFAs and include prostaglandins and leukotrienes. Eicosanoids can act as inflammatory mediators.³⁰ Arachidonic acid in plasma membranes serves as a substrate for production of eicosanoids of the 2-series of prostaglandins and 4-series of leukotrienes by the action of cyclooxygenases and lipoxygenases.^{15,16,31} In contrast, EPA and DHA in plasma membranes result in production of different eicosanoids (mainly the 3-series of prostaglandins and 5-series of leukotrienes) that are less proinflammatory compared with those derived from AA.^{15,16,31} The production of these less proinflammatory eicosanoids results in EPA and DHA being characterized as anti-inflammatory. These effects can be observed after dietary supplementation with omega-3 fatty acids and after incorporation into plasma membranes of tissues.³²

When fish oil omega-3 fatty acids are administered, they can be given as a supplement separate from the diet (such as a liquid or capsule containing fish oil) or as part of the animal's diet. The amount of omega-3 fatty acids supplemented can be expressed as an absolute amount (total milligrams of EPA and DHA), a milligram per kilogram dosage, or as a dietary omega-6 to omega-3 (n-6:n-3) ratio. The total n-6:n-3 should be used with caution, because it does not reflect the total amount of omega-3 fatty acids present in the diet or the type of omega-3 fatty acids present.

The total n-6:n-3 ratio has been used extensively in reports because there is competition between LA and ALA for enzymes that desaturate and elongate these fatty acids.³³ However, this ratio should be used with

care because, in most instances, it is calculated using total omega-3 fatty acids (ALA, EPA, and DHA). The use of the total omega-3 concentration is not bioequivalent to the EPA and DHA concentration, because of the poor conversion of ALA to EPA and DHA and because ALA does not have the same biologic effects as the long-chain omega-3 PUFAs. Consequently, many researchers consider the total intake of the individual omega-6 and omega-3 fatty acids to be more important than their ratio.^{33,34} The n-6:n-3 ratio can be altered in several ways. The omega-3 fatty acid concentration could be increased, decreased, or unchanged resulting in either an increase or decrease in the n-6:n-3 ratio. Waldron et al found that in dogs fed 2 different diets with the same n-6:n-3 ratio but with different sources of omega-3 fatty acids (linseed oil versus menhaden fish oil), neutrophil function was affected differently.³⁵ Thus, the type and amount of omega-3 fatty acids are likely more influential compared with the total n-6:n-3 ratio.

Although the n-6:n-3 ratio has been used primarily in many of the studies described in this review, to the extent possible and when reported, it will be pointed out when long-chain omega-3 PUFAs were used, when an unknown combination of ALA and long-chain omega-3 PUFAs was used, and how the ratio was calculated. Many of these adverse effects are theoretical at this time. The fact that many of the studies cited used the n-6:n-3 ratio as opposed to specifying the total omega-3 fatty acid dosage or EPA and DHA concentration make the results of many of the studies difficult to interpret with respect to actual amounts used.

Altered Platelet Function

In addition to serving as a substrate for the production of eicosanoids via cyclooxygenases and lipoxygenases, the presence of AA in phospholipid membranes also results in production of thromboxane A₂, a potent platelet activator. Thromboxane A₂ is essential for normal platelet function.³⁶ The presence of EPA and DHA leads to production of thromboxane A₃, which is a less potent platelet activator than thromboxane A₂.^{37,38} Supplementation of EPA and DHA, therefore, may affect platelet activation and function differently than omega-6 fatty acid supplementation because of the different eicosanoids produced.

Decreased platelet activity and aggregation has been detected in humans supplemented with EPA and DHA and may lead to an antithrombotic effect. Guillot et al dosed healthy adult men with 200–1,600 mg DHA for 8 weeks and reported decreased platelet reactivity,³⁹ whereas Wensing et al dosed healthy elderly humans with 1.6 g EPA and DHA for 6 weeks and reported decreased *ex vivo* platelet aggregation.⁴⁰

The effects of omega-3 fatty acids on coagulation also have been examined in cats and dogs. Two studies have involved cats,^{38,41} and the results were mixed. Saker et al noted prolonged bleeding time and

decreased platelet aggregation in cats after supplementation with omega-3 fatty acids at an n-6:n-3 ratio of 1.3:1 for 16 weeks.³⁸ The actual dosage of omega-6 and omega-3 fatty acids was not mentioned in this study, making results difficult to interpret. Bright et al did not document a measurable effect on hemostasis after supplementation of cats with EPA and DHA for 8 weeks (1.126 g EPA and 0.624 g DHA per day for 4 weeks, then 1.689 g EPA and 0.936 g DHA per day for 4 weeks).⁴¹ This is a very large dose of EPA and DHA (1,800–2,800 mg/day, which is equivalent to nine 1,000-mg capsules of typical fish oil or 2 teaspoons of liquid fish oil daily).

The effects of EPA and DHA have been examined in dogs and have revealed either only small changes or no change in platelet aggregation. Boudreaux et al fed laboratory dogs diets with differing n-6:n-3 ratios for 12 weeks, with the lowest at an n-6:n-3 ratio of 5:1, and did note small changes in platelet reactivity, but did not consider them clinically relevant. No total dose of omega-3 fatty acids, but only the n-6:n-3 ratio,³⁷ was reported in this study. LeBlanc et al fed laboratory dogs diets with an n-6:n-3 ratio of 3.4:1 with or without vitamin E (again, no total dose was reported) for 12 weeks and saw no significant effects on platelet function.²⁵ McNeil et al fed a diet with fish oil (EPA, 29 g/kg diet and DHA, 24 g/kg diet on dry matter basis) and arginine at $140 \times \text{BW}(\text{kg})^{0.75}$ kcal metabolizable energy per day to dogs with naturally occurring lymphoma and hemangiosarcoma and did not see an effect on platelet aggregation or platelet count when compared with dogs with the same malignancies fed with a control diet rich in omega-6 fatty acids.⁴² In addition, the investigators did not note clinical bleeding at venipuncture sites or during catheter placement.⁴²

Although changes in platelet function were not seen in all 3 of the studies performed in dogs, 2 of them^{25,37} did not report the total amount of omega-3 fatty acids fed, just the total n-6:n-3 ratio. Many commercial products contain unknown amounts of ALA, making results difficult to interpret. In addition, all of the studies that are currently available for review use platelet aggregometry, although other instruments such as thromboelastography platelet mapping and platelet function analyzers currently exist.^{43,44} The more recently available instrumentation may be more sensitive for detecting slight changes in platelet function. Future studies using defined amounts of either ALA or EPA and DHA and more sophisticated instrumentation will be needed to better determine any effects omega-3 fatty acids have on platelet function.

Although omega-3 fatty acid supplements can decrease platelet aggregation, a clinically relevant effect on bleeding in normal humans is not expected.⁴⁵ Therefore, even if there were a measurable effect of omega-3 fatty acids on hemostasis in dogs or cats using different instrumentation, it may not be immediately clinically relevant. However, if mildly decreased platelet function in omega-3 fatty acid supplemented companion animal patients is combined with thrombocytopenia caused by

disease, the mild decrease in platelet function could become clinically relevant.

Gastrointestinal Adverse Effects

Adverse gastrointestinal effects are seen frequently and are commonly reported in clinical patients supplemented with dietary omega-3 fatty acids. With veterinarians using high dosages of omega-3 fatty acids to treat clinical disease (up to EPA and DHA = 53 g/kg diet on dry matter basis)^{1,42} adverse gastrointestinal effects are a concern. If fatty acids are undigested, they pass into the upper gastrointestinal tract where they can act as a substrate for bacteria, and this dietary fat may result in secretory diarrhea.^{46,47} Dogs that receive omega-3 fatty acid supplements have been reported to develop diarrhea as an adverse effect. Adverse gastrointestinal effects, including diarrhea and vomiting, are reported as a reason for discontinuing supplementation in research studies.^{4,13} Clinical patients also develop gastrointestinal signs after supplementation. Roubush et al. reported that as many as 10% of dogs with neoplastic disease that were fed a high-fat canned diet rich in omega-3 fatty acids in conjunction with other cancer therapy developed an abnormal feces consistency.⁴⁸ Development of adverse gastrointestinal effects can occur even more frequently than reported, but the effects are dose-dependent. Recommendations for management of diarrhea associated with omega-3 fatty acid supplementation include slowly transitioning the animal to the high fat diet (or to a high dose of a dietary fat supplement such as concentrated omega-3 fatty acids), adding fiber to the diet, or using antibiotics.⁴⁸ Probiotics or prebiotics also could be used. Clinical patients that develop diarrhea or other adverse gastrointestinal effects may need a decreased dosage of omega-3 fatty acids as well as other dietary modification.

Pancreatitis also is a concern when feeding high fat diets or high doses of fatty acid supplementation, especially in dogs with a known risk of pancreatitis. However, there are no reports of omega-3 fatty acid or fish oil supplements causing pancreatitis in dogs, cats, or humans. Theoretically, omega-3 fatty acids could prevent pancreatitis because of decreased blood triglyceride concentrations. An extremely high dosage of omega-3 fatty acids or a fish oil supplement in addition to a very high fat diet would likely be required to induce pancreatitis.

Detrimental Effects on Wound Healing

The stages of wound healing include inflammation, repair, and maturation.⁴⁹ Although omega-3 fatty acids are beneficial for management of inflammatory diseases because of their anti-inflammatory properties, wound healing is dependent on some degree of inflammation. The inflammatory stage of wound healing is characterized by migration of leukocytes into the wounded area and is initiated within 6 hours of trauma. Cytokines are involved in this process and are

essential for attracting leukocytes to the area.⁴⁹ Because inflammation is essential for the process of wound healing, decreasing inflammation with omega-3 fatty acids could be detrimental to patients with extensive wounds caused by trauma or in the postoperative period. This is a problem that could occur in addition to effects of omega-3 fatty acids on hemostasis.

Numerous studies have been performed in rats in which researchers investigated the effects of supplemental omega-3 fatty acids on wound healing. As a whole, results are conflicting. Albina et al⁵⁰ and Otranto et al⁵¹ reported that feeding rats with diets rich in omega-3 fatty acids resulted in delayed wound healing. However, in another study, Gercek et al did not observe detrimental effects on wound healing after parenteral fish oil infusion in dexamethasone-treated rats.⁵²

Results from studies using companion animals suggest that wound healing is not affected by omega-3 fatty acid supplementation.^{53–55} Corbee et al used an omega-3 fatty acid-enriched diet in client-owned cats with feline chronic gingivitis and stomatitis and did not see an effect on the degree of inflammation or wound healing. However, the percentage of EPA and DHA in the enriched diet was relatively low (0.83% versus 0.10% in the control diet).⁵³ Mooney et al made small wounds in purpose-bred dogs and did not observe an effect of dietary omega-3 fatty acids on wound healing.⁵⁴ In these studies, the n-6:n-3 ratio was the main method of reporting dietary omega-3 fatty acids. The n-6:n-3 ratios ranged from 10:1 to 40:1 (Corbee et al; EPA = 0.03–0.46% of total fatty acids, DHA = 0.07–0.37%) or from 5:1 to 100:1 (Mooney et al; omega-3 fatty acids from fish oil and flaxseed oil = 0.4–3.4% of total fatty acids), which are higher ratios than that used by Albina et al (<1:1). The ratios do not give accurate information on the EPA and DHA concentration of the diet. The diet with the lower n-6:n-3 ratio in the Corbee et al study contained added fish oil, but not flaxseed oil. Mooney et al used a combination of fish oil and flaxseed oil to produce the final n-6:n-3 ratio reported. In another study on omega-3 fatty acid supplementation and wound healing, Scardino et al used a diet with an n-6:n-3 ratio of 0.3:1 and supplemented purpose-bred dogs for 30 days before wound formation.⁵⁵ In this study, the dogs consuming the omega-3 fatty acid-enriched diet, which contained menhaden fish oil as the source of omega-3 fatty acids (actual dose not reported), had less epithelialization of open wounds after 5 days. There were no differences compared with the dogs consuming the control diet supplemented with soya oil after 10 days. These authors suggest that there may be short term, but not long-term effects on wound healing with high amounts of omega-3 fatty acid supplementation.

Potential for adverse effects on wound healing may be greatest immediately after trauma or surgery. The effect on wound healing likely depends on the amount and type of dietary omega-3 fatty acids, the duration of supplementation, and the severity of the wound.

Given these results, it may be wise to discontinue high doses of omega-3 fatty acids (either dietary or supplemental) before surgery to avoid interference with inflammation and wound healing.

Lipid Peroxidation

Lipid peroxidation is characterized by a free radical attack on an unsaturated fatty acid and can occur in the presence of oxygen.⁵⁶ Long-chain highly unsaturated fatty acids such as EPA, DHA, and AA are at high risk to undergo peroxidation. When fish oil omega-3 fatty acids are supplemented, EPA and DHA accumulate in cell membranes. If antioxidants are not provided at adequate concentrations, membrane phospholipid fatty acids can be vulnerable to peroxidation and free radicals can form as a result.⁵⁷ Lipid peroxidation can be detrimental because of effects on the stability of cell membranes and also as a result of free radical attacks on proteins and DNA.^{18,56}

Lipid peroxidation and free radical and other by-product formation potentially could negatively affect patient tolerance of dietary supplements.⁴⁵ Fish oil is especially unstable because of the highly unsaturated fatty acids (EPA and DHA) in fish oil preparations. Effects of lipid peroxidation can be avoided by supplementing diets enriched in omega-3 fatty acids with antioxidants such as vitamin E or by adding vitamin E to omega-3 fatty acid purified supplements.^{18,57} Peroxidation can occur in both the product itself and within the body. Adding vitamin E (specifically alpha-tocopherol) to supplements can decrease lipid peroxidation and thus limit rancidity and increase freshness and shelf-life of supplements.⁴⁵ Vitamin E is a hydrogen donor to free radicals and prevents oxidative damage to PUFAs in membranes.²⁸ Because of the high risk for lipid peroxidation, it is prudent to check supplements for adequate amounts of antioxidants. It may be necessary to call the manufacturer to obtain this information.

Studies on the effects of omega-3 fatty acids on lipid peroxidation are conflicting. LeBlanc et al noted no change in plasma lipid oxidative byproduct concentrations after 12 weeks of fish oil supplementation to young dogs (n-6:n-3 = 3.4:1, EPA = 1.75 g/kg diet and DHA = 2.2 g/kg diet on dry matter basis).²⁵ In another study by LeBlanc et al, no changes were noted in plasma lipid peroxide concentrations feeding dogs the same diet the same amount of time as in the aforementioned study.⁵⁸ Wander et al. noted increased amounts of lipid oxidative by-products (plasma and urine thiobarbituric reactive substances) after supplementing dogs with fish oil at a dietary n-6:n-3 ratio of 5.4:1 (ALA = 0.7 g/kg diet, EPA = 1.05 g/kg diet, and DHA = 0.95 g/kg diet) and 1.4:1 (ALA = 0.85 g/kg diet, EPA = 3.0 g/kg diet, and DHA = 2.65 g/kg diet). No adverse effects were noted in these dogs.⁵⁷

Although the clinical adverse effects of lipid peroxidation are somewhat unclear, they may be manifested as vitamin E deficiency. Wander et al noted decreased

plasma vitamin E concentration in dogs fed a diet enriched with fish oil using an n-6:n-3 ratio of 1.4:1.⁵⁷ Both the amount of long-chain PUFAs in a supplement or in the patient's diet and the degree of peroxidation that occurs before consumption can affect requirements for vitamin E.²⁸ Dietary vitamin E requirements increase with high concentrations of dietary PUFAs.^{28,59} Signs of vitamin E deficiency include muscle weakness caused by muscle degeneration, retinal degeneration, and steatitis, especially in cats.²⁸ Some authors suggest that cats will refuse diets containing peroxidized lipids⁶⁰; however, there are reports of cats developing pancreatitis after consuming oily fish-based diets.⁶¹

Potential for Toxin Exposure and Nutrient Excess

Supplementation of fish oil has the potential to expose patients to environmental toxins. Consumption of high quantities of fish or fish oil can increase exposure to heavy metals such as mercury or chemicals such as polychlorinated biphenyls and polychlorodibenzodioxins.^{18,45} However, it appears that the risk of toxin exposure and related clinical signs is low overall.⁴⁵ In Inuit preschool-aged children (in a population that consumes a large amount of fish), prenatal exposure to mercury, polychlorinated biphenyls, and pesticides did not cause adverse effects on neurologic function.⁶² Fish-based diets and fish oil supplements, when fed on long term, could potentially cause mercury toxicity.⁶³ Clinical signs are more common in cats than dogs because of the frequency of feeding fish-based diets to cats, and include anorexia, ataxia, blindness, and seizures.⁶⁴ Clinical signs of mercury toxicity in dogs include neurologic dysfunction, gastrointestinal signs including vomiting and death.⁶⁵

Hypervitaminosis is a concern with fish oil supplements such as cod liver oil, especially when they are supplemented at high dosages. Fat-soluble vitamins, especially vitamins D and A, are more of a concern than water-soluble vitamins because most water-soluble vitamins do not accumulate in tissue. There have been no reports in humans of vitamin D or A toxicity associated with fish oil supplementation and although the potential for toxicity exists, it is low.^{45,66} Even at a high dosage of supplementation such as 220 mg fish oil per kilogram body weight it would be difficult to reach the safe upper limit for vitamins D and A. The safe upper limits for a 10 kg dog are 14.6 µg cholecalciferol (584 international units) and 11,804 retinol equivalents of vitamin A.²⁸

Overall, with the diversity of therapeutic uses for fish oil, the benefits of fish oil intake likely outweigh the risks of toxin exposure and nutrient excess. Veterinarians should inquire about the mercury and toxin concentrations of fish oil supplements before prescribing them to clinical patients. Contacting the manufacturer may be necessary to ascertain this information.

Weight Gain

Although weight gain is not a commonly noted adverse effect of omega-3 fatty acid supplementation, the calories that oil contains should be a concern. Fat is the most energy dense nutrient when compared with protein or carbohydrate, and each gram of oil contains about 9 kcal.⁶⁷ One teaspoon (5 ml) of oil contains about 42 kcal.⁶⁷ Weight gain could occur when large dosages of omega-3 fatty acids are recommended, such as for dogs with osteoarthritis or neoplastic disease. Published recommendations for dogs with neoplastic disease include adding 12–20 fish oil capsules per day for a 10 kg dog.⁴⁸ This represents 108–180 kcal of fish oil per day whereas the resting energy requirements for a 10 kg dog are <400 kcal/day. In many dogs, especially in obese or obesity-prone dogs, veterinarians must be cautious about the addition of large dosages of omega-3 fatty acids, either in the diet or supplemented in addition to the diet. The calories that are in the oil should be accounted for when developing a nutrition plan for these animals and if a large quantity of omega-3 fatty acids is supplemented in addition to the diet, it may unbalance the pet's diet. One way to avoid this issue is to use a commercial diet that is supplemented with omega-3 fatty acids at the desired dosage. However, it is difficult to find a commercial diet containing sufficient concentrations of EPA and DHA.

Altered Immune Function

Inflammatory mediators such as prostaglandins and leukotrienes are involved in the immune response, and suppressing production of the "proinflammatory" forms of these products by supplementation of omega-3 fatty acids can alter immune function. Neutrophil functions that are mediated by leukotriene B₄ can be inhibited by supplementing fish oil omega-3 fatty acids. Lee et al supplemented healthy human subjects with 5.4 g EPA and DHA daily and noted decreased production of leukotriene B₄ as well as decreased chemotactic responses and adherence of neutrophils.⁶⁸ Vaughn et al noted similar effects in dogs. After supplementing various concentrations of dietary omega-3 fatty acids from menhaden oil and flaxseed to produce n-6:n-3 ratios of 5:1, 10:1, 25:1, 50:1, and 100:1 for 12 weeks, skin and neutrophil leukotriene B₄ concentrations were decreased whereas leukotriene B₅ concentrations were increased in the dogs consuming higher levels of dietary omega-3 fatty acids.⁶⁹ Waldron et al investigated the effects of diets enriched in linseed oil and fish oil on neutrophil leukotriene B₄ production. In this study, dogs fed with diets containing more EPA and DHA (the fish oil-supplemented diet, EPA = 3.07% diet on an as fed basis, DHA = 1.00%) had significantly lower neutrophil leukotriene B₄ production compared with dogs fed with the linseed oil-supplemented diet. In addition, dogs consuming menhaden fish oil had higher leukotriene B₅ production compared with dogs consuming linseed oil, despite the fact that the 2 diets had nearly identical n-6:n-3

ratios.³⁵ However, the *ex vivo* nature of these studies makes determining clinical relevance of the changes in leukotriene concentrations difficult. Neutrophil function was not measured. Leukotriene B₄ is an initiator of neutrophil recruitment, chemotaxis, and degranulation, whereas leukotriene B₅ is a less active ligand at the leukotriene B receptor.^{68,69} The Waldron et al study³⁵ provides evidence supporting the idea that not all omega-3 fatty acids are equal and that fatty acid composition is more important than total n-6:n-3 ratio. Diets supplemented with ALA are not biologically equivalent to diets supplemented with EPA and DHA.

Omega-3 fatty acid supplementation also can affect hypersensitivity reactions as measured by the results of the delayed-type hypersensitivity (DTH) test. In the previously mentioned Wander et al study, researchers fed healthy geriatric Beagles diets with n-6:n-3 ratios of 31:1, 5.4:1, and 1:1 (the lower n-6:n-3 diets were supplemented with fish oil) and noted a lower DTH response in the group consuming a n-6:n-3 ratio of 1.4:1 versus a n-6:n-3 ratio of 5.4:1 or 31:1.⁵⁷ Hall et al fed healthy geriatric Beagles diets with n-6:n-3 ratios of approximately 40:1 and 1.4:1 with varying concentrations of vitamin E (alpha-tocopherol) and noted a suppressed DTH response in dogs fed with the lower n-6:n-3 ratio, regardless of the concentration of dietary vitamin E. The lower n-6:n-3 ratio was created by adding fish oil. In this study, antibody titers against a foreign protein were unaffected by diet.⁷⁰

There are other potential mechanisms of altered immune function after omega-3 fatty acid supplementation. Lymphocyte numbers also may be affected. In another study by Hall et al, geriatric Beagles were fed diets with 3 different n-6:n-3 ratios (31:1, 5.4:1, and 1.4:1) for 11 weeks. Fish oil was the source of the omega-3 fatty acids in the diets with lower n-6:n-3 ratios. The dogs fed with the diet with a n-6:n-3 ratio of 1.4:1 (EPA = 3.0 g/kg diet and DHA = 2.75 g/kg) had higher total lymphocyte counts but lower CD4⁺ T lymphocyte counts, and lower CD4⁺ to CD8⁺ ratios after vaccination with foreign proteins when compared with dogs fed with lower dietary concentrations of omega-3 fatty acids.⁷¹ The clinical relevance of this decrease is uncertain despite its statistical significance. Hall et al also noted that neutrophil bactericidal activity was unaffected by dietary fish oil supplementation at varying concentrations up to EPA = 0.25% of diet on an *ad libitum* basis and DHA = 0.17% in healthy dogs.⁷² LeBlanc et al fed dogs with a diet enriched in fish oil with a n-6:n-3 ratio of 3.4:1 (EPA = 1.75 g/kg diet, DHA = 2.2 g/kg) and noted decreased lymphocyte proliferation as measured using flow cytometry after 12 weeks.⁵⁸

There are fewer studies published on the effects of dietary fatty acid manipulation on immune function in cats, but results are similar to those studies performed in dogs. Park et al supplemented flaxseed oil and fish oil at a n-6:n-3 ratio of 5:1 and noted higher skin leukotriene B₅ concentration in the cats fed higher dietary concentrations of fish oil, suggesting that fish oil (containing EPA and DHA) is more

immunosuppressive than flaxseed oil (containing ALA).⁷³ These results are similar to those of the Waldron et al study³⁵ in the sense that results from both studies suggest that different omega-3 fatty acids have different effects.

Although the effects of omega-3 fatty acid supplementation on immune function are not clearly known, there is potential for altered immune function with supplementation of omega-3 fatty acids. Whether the changes noted in the aforementioned studies are clinically relevant remains unknown.

Effects on Glycemic Control and Insulin Sensitivity

In an earlier review article on adverse effects of omega-3 fatty acid supplementation, hyperglycemia was listed as a potential adverse effect.¹⁸ Results of early studies performed with human subjects are mixed, with some authors suggesting that omega-3 fatty acid supplementation causes hyperglycemia and others indicating that omega-3 fatty acids may actually improve insulin sensitivity and glycemic control. Glauber et al⁷⁴ noted a significant increase in fasting blood glucose concentration after 1 month of dietary supplementation with omega-3 fatty acids. Feskens et al,⁷⁵ on the contrary, noted a protective effect of fish intake against the development of impaired glucose tolerance and diabetes mellitus in elderly human subjects. In another study, dietary omega-3 fatty acid supplementation during energy restriction resulted in improved insulin sensitivity in overweight and obese young adults.⁷⁶

In cats, authors suggest that dietary supplementation of omega-3 fatty acids results in improved insulin sensitivity. In one study by Wilkins et al, the authors concluded that in obese research cats, a diet with supplemented omega-3 fatty acids appeared to maintain insulin sensitivity.⁷⁷ In this study, the omega-3 fatty acid-enriched diet contained 1.01% ALA, 3.91% EPA, and 4.72% DHA (percentages indicate percent of dietary fatty acids). The control (saturated fatty acid) diet contained 0.68% ALA, 0.37% EPA, and 0.46% DHA.⁷⁷ Another group found correlations between serum EPA concentrations and serum insulin concentrations in obese cats.⁷⁸ Cats that had significantly higher serum EPA concentrations had lower insulin concentrations and vice versa. These were client-owned cats and were not consuming a standardized diet.

Although it does not appear that supplementation of omega-3 fatty acids causes hyperglycemia in cats, more studies are needed before omega-3 fatty acids are recommended to diabetic patients, especially dogs. In addition, although improved insulin sensitivity would be beneficial in many patients, caution should be used in diabetic patients receiving insulin and concurrent omega-3 fatty acid supplementation.

Nutrient–Drug Interactions

In addition to direct adverse effects from omega-3 fatty acids, there is potential for nutrient-drug interac-

tions. In humans, omega-3 fatty acids can interact with simvastatin to decrease blood lipid concentrations.⁷⁹ In companion animals, the efficacy of some drugs, including doxorubicin, has been investigated with omega-3 fatty acid supplementation. Omega-3 fatty acids did not affect doxorubicin pharmacokinetics in a study performed in dogs.⁸⁰ For other drugs, nutrient-drug interactions may exacerbate adverse effects that can occur with omega-3 fatty acid supplementation alone, or they may create other adverse effects not listed above. In humans, omega-3 fatty acids and aspirin have a synergistic effect on bleeding times when supplemented together.⁸¹ Although it seems as though aspirin and omega-3 fatty acids affect platelet function in different manners (irreversible inhibition versus competitive inhibition with AA),⁸¹ the synergistic effect of aspirin and omega-3 fatty acids on platelet function is an example of a nutrient-drug interaction. Given the frequency of omega-3 fatty acid supplementation in conjunction with nonsteroidal anti-inflammatory drug administration,¹⁴ this is one possible area for nutrient-drug interactions in dogs. Carprofen administration has been demonstrated to affect hemostasis as measured using thromboelastography.⁸² Concurrent administration of carprofen and omega-3 fatty acids potentially could negatively impact hemostasis similar to the combination of aspirin and omega-3 fatty acids in humans. Omega-3 fatty acids and clopidogrel may interact in a similar manner.

Conclusion

Currently, omega-3 fatty acids are used in managing many diseases including neoplasia,¹ dermatologic disease,²⁻⁴ hyperlipidemia,^{5,6} cardiovascular disease,^{7,8} renal disease,^{9,10} gastrointestinal disease,¹¹ and orthopedic disease.¹³⁻¹⁶ There are other disease processes or conditions for which they may be beneficial, including neurologic diseases,⁸³ asthma,⁸⁴ and behavioral issues.⁸⁵ The therapeutic effects of fish oil are discussed elsewhere.⁸⁶

Adverse effects, if observed, are likely to be dose-dependent. It is necessary to understand dosages of omega-3 fatty acids to understand how much fish oil to supplement, or what dietary concentration to aim for when recommending omega-3 supplementation. Provision of omega-3 fatty acids can be expressed as milligrams of total omega-3 fatty acids per kilogram body weight; as milligrams of EPA and DHA per kilogram body weight or metabolic body weight; as a dietary amount on a per energy basis (grams or milligrams per 100 or per 1,000 kcal); or as a dietary amount on a per weight basis (grams or milligrams per 100 grams of diet as fed or on dry matter basis). The amount of omega-3 fatty acids also can be expressed as a ratio of n-6:n-3 fatty acids, or as a ratio of "functional" fatty acids (LA + AA:EPA + DHA). The same enzymes are involved in metabolism of omega-6 and omega-3 fatty acids, resulting in competition between these fatty acids for incorporation into cell membranes

and other biological properties. Therefore, dietary excess or deficiency of LA versus ALA may influence conversion rates to downstream products. Dietary amounts of omega-6 versus omega-3 fatty acids are frequently expressed as a dietary n-6:n-3 ratio in addition to absolute amounts for this reason. However, ALA is not equivalent to EPA and DHA and the total n-6:n-3 ratio by itself does not accurately describe the fatty acid composition of the diet. A product with a high total omega-3 fatty acid concentration could contain high concentrations of ALA, high concentrations of EPA and DHA, or a combination of these fatty acids. Because diets with ALA have different effects when compared with diets enriched in EPA and DHA, the type of omega-3 fatty acids is crucial information and the lack of distinction between these fatty acids may contribute to the equivocal nature of results of earlier studies.

Unfortunately, all drugs, dietary supplements, or nutraceuticals have the potential for adverse effects. Despite the benefits listed above, there are potential risks associated with usage of omega-3 fatty acids. Clinicians should understand the adverse effects that may occur with omega-3 fatty acid supplementation, and that potential risks should be assessed in conjunction with the potential benefits. The National Research Council publication on Nutrient Requirements of Dogs and Cats indicates a safe upper limit of the combined amounts of EPA + DHA as 2,800 mg/1,000 kcal of diet, equivalent to 370 mg per (kg body weight)^{0.75} for dogs.²⁸ This is equivalent to 2,080 mg for a 10 kg dog. Presently, not enough published data are available to set a safe upper limit for cats.

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