



# Timely Topics in Nutrition

## Responses of dogs to dietary omega-3 fatty acids

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**M**odification of metabolic responses for cholesterol and other lipids as a result of dietary methods or drugs has been extensively studied in humans and laboratory animals, and much has been published on this topic. However, less is known about this topic in small companion animals, such as dogs and cats. One of the reasons is that compared to humans, cats and dogs are typically resistant to coronary artery disease, myocardial infarction, cerebral vascular stroke, and atherosclerosis. Thus, they are rarely studied in regard to these disorders. Nonetheless, dogs are especially useful in the evaluation of compounds that lead to important discoveries of drugs for humans. Therefore, knowledge of canine cholesterol, fatty acid, and lipoprotein metabolism must be understood for these comparative purposes.

Furthermore, the evolution of veterinary practice and increases in the human-animal bond for dogs and cats and subsequent high level of veterinary care have emphasized ongoing interest in effective ways to promote healthy growth and longevity in these animals, similar to improvements for human health. Indeed, pet owners often attempt to provide care for their pets that is equivalent to their own care. Thus, similarities and differences among these species should be understood as new modalities of dietary modification or drug action make their way into veterinary medicine.

Several disorders relating to lipid metabolism of dogs and cats are similar to those in humans. These include obesity, diabetes mellitus, renal disease, some cardiovascular disorders, and hypothyroidism<sup>1</sup>; hence, numerous parallel approaches to manage patients with these disorders exist. For example, evidence exists to support the role of long-chain omega-3 fatty acids in renal and cardiovascular disorders in humans and companion animals. Although renal disorders are typically multifaceted, to the extent that hypertension is involved, fish oil supplements in dogs appear to help preserve renal function.<sup>2</sup> Similarly, in cardiovascular health, research in dogs has revealed that fish oils have an antiarrhythmic effect<sup>3</sup> and can minimize loss of heart muscle in dogs with congestive heart failure.<sup>4</sup>

### ABBREVIATIONS

ALA	$\alpha$ -Linolenic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
LA	Linoleic acid
DPA	Docosapentaenoic acid
PG	Prostaglandin
PUFA	Polyunsaturated fatty acid

An approach for the study of lipid metabolic responses has been to first understand the effects of dietary modification in clinically normal animals. Knowledge generated in this manner enables assessment of dietary benefits in healthy companion animals. In addition, it enables better interpretation of diet-disease interactions when opportunities arise. More specifically, our laboratory group has been interested in the effects of omega-3 fatty acid metabolism in dogs during various life stages. The information provided here will focus on several aspects of studies on omega-3 fatty acids, including the capacity of dogs to metabolize omega-3 fatty acids, effects of omega-3 fatty acids on skin and coat, inflammatory responses, and neurologic development in puppies.

### Conversion of ALA (18:3n-3) to EPA (20:5n-3) and DHA (22:6n-3) in Adult Dogs

A study<sup>5</sup> was conducted in which a complete and balanced commercial, dry-extruded diet was supplemented with 3% (wt:wt) ground sunflower seed (rich in omega-6) or 3% (wt:wt) ground flaxseed (rich in omega-3) and fed to dogs for 84 days. The sunflower diet contained 9.3% of calories as LA and 0.4% of calories as ALA, whereas the flaxseed diet had 7.3% of calories as LA and 2.5% of calories as ALA. Blood samples collected at selected time points allowed determination of plasma patterns of phospholipid fatty acid. Rapid accumulation of EPA was evident (4 days after onset of feeding of the flaxseed diet), and EPA accumulation appeared to reach a steady-state plasma concentration by 28 days. In addition, DPA (22:5n-3), a precursor of DHA, was also detected (**Figure 1**). However, no accumulation of DHA was detected. Because little or no DHA accumulated in plasma, it was speculated that hepatic synthesis of DHA may be limited. Instead, transport of DPA synthesized from dietary ALA may be

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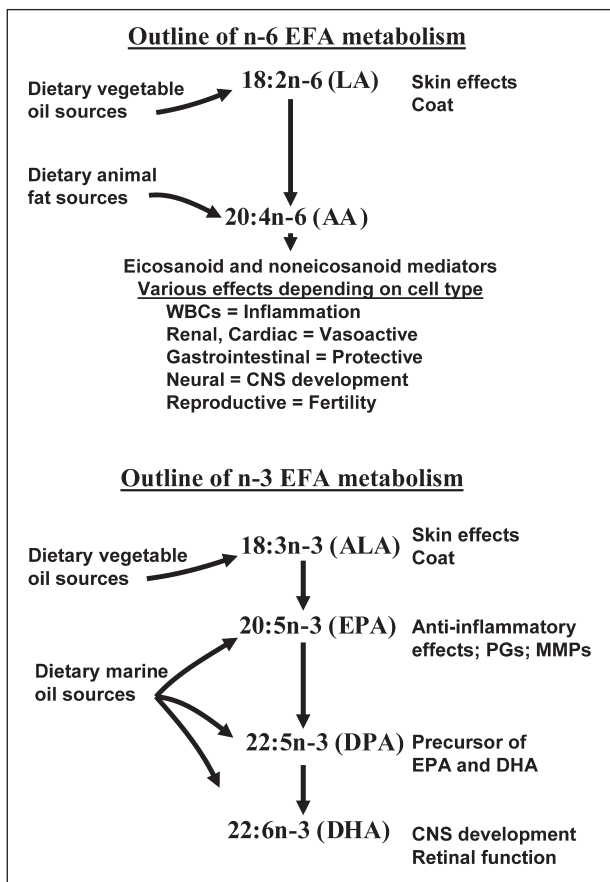


Figure 1—Outline of metabolism of n-6 (omega-6; top) and n-3 (omega-3; bottom) fatty acids. AA = Arachidonic acid. MMP = Matrix metalloproteinase.

delivered to cells, such as those in nerve tissues, that readily convert this precursor fatty acid to DHA.<sup>6</sup> As such, DPA would have a role as a circulating substrate reservoir for DHA synthesis. Alternatively, DPA could be retroconverted via partial  $\beta$ -oxidation to form EPA when taken up by other metabolically active tissues, such as platelets or neutrophils, for eicosanoid, PG, or leukotriene production unique to each particular cell type.<sup>7-10</sup>

The aforementioned study<sup>5</sup> was the first in which it was determined that EPA concentrations detected in dogs after feeding of ALA was likely the result of synthesis, even though amounts provided by conversion appeared to be small. Additional questions remained, such as whether ALA or its derived EPA could help modify the appearance of the skin or coat and whether a beneficial effect on the inflammatory response may exist.

### Effects of ALA, Total Fat, and LA on Skin and Coat of Clinically Normal Dogs

During that same study,<sup>5</sup> a separate study<sup>11</sup> was conducted in which the condition of the skin and coat of the dogs was scored. Improvements of skin and coat were found after 28 days for dogs of both groups. However, differences attributable to a specific diet were not evident, and improvements were not sustained, prob-

ably because of dietary adaptations. Of particular interest, however, was that dogs fed the flaxseed diet accumulated more LA than did dogs fed the sunflower diet, even though the sunflower diet contained more LA. It was speculated that there was a sparing effect of ALA on LA with resultant improvements in skin and coat; another possibility was the effects of total fat. Subsequent studies on skin and coat have yielded similar results, described below.

Another study<sup>a</sup> on skin and coat was conducted to compare effects of 3 dry-extruded diets. In that study, after feeding an acclimation diet, a diet with adequate essential fatty acid content, a diet containing high amounts of LA, and a diet containing high amounts of LA plus ALA were fed. All 3 of those diets had a higher fat content (approx 13% on an as-is basis), compared with the fat content for the acclimation diet, which was approximately 9% on an as-is basis. Compared with results for the acclimation diet, all 3 diets resulted in an improvement in skin and coat scores, and the improvement was significant  $\geq 7$  weeks after onset of feeding. Significant improvements were observed in coat glossiness and softness when these test diets were fed. Metabolically, however, fatty acid patterns of plasma phospholipid fractions again revealed a sparing effect of ALA on LA. It should be mentioned that a direct effect of ALA on improvements of skin and coat could not completely be ruled out in these studies.

Furthermore, the improvements appeared to be attributable, at least in part, to the higher total dietary fat concentrations of the diets. Although other benefits to the skin and coat are attributable to dietary polyunsaturated fats, the more dramatic effect on skin in these studies appeared to be as a result of total fat content. Nonetheless, the appropriate balance of PUFAs provides additional benefits beyond skin and coat, as indicated in other studies in dogs. Thus, the aforementioned findings do not preclude the benefits of including polyunsaturated fats in modern commercial diets for dogs.

### Modification of the Inflammatory Response

Long-chain n-3 PUFAs from fish oil or other marine sources appear to be especially capable of modifying inflammatory and immune responses.<sup>12-14</sup> However, on the basis of findings in dogs and similar data in other species, including humans, diets containing only ALA as a source of n-3 fatty acids may not perform as effectively when included on an equivalent-weight basis.<sup>15,16,b</sup> One reason is the inefficient rate of conversion of ALA to EPA.<sup>17,18</sup>

To investigate neutrophil-mediated inflammatory responses in dogs, diets containing high supplemental concentrations of ALA from flaxseed oil, EPA from fish oil, beef tallow, and safflower oil were prepared.<sup>b</sup> The resultant fish oil and flaxseed diets contained nearly identical ratios of total omega-6 to total omega-3 content (0.34 vs 0.38 for fish oil and flaxseed, respectively). Results from this study<sup>b</sup> included both structural and functional changes of isolated neutrophils. Both fish oil and flaxseed diets caused an increase in incorporation of long-chain omega-3 fatty acids into neu-

trophil membranes, but to differing extents. The EPA enrichment was greater in the fish oil group, and no DHA was detected in the flaxseed group. As a result of this differential enrichment, isolated neutrophils from the dogs fed the fish oil diet had less leukotriene B<sub>4</sub> and more leukotriene B<sub>5</sub> than did the other 3 groups. The flaxseed group also had a reduction of leukotriene B<sub>4</sub> content and higher production of leukotriene B<sub>5</sub>, compared with results for dogs fed diets containing beef tallow and safflower; however, again, it was not to the same extent as dogs fed the fish oil-supplemented diet. Both flaxseed and fish oil groups had similar superoxide production and improvements in ex vivo phagocytosis. In both groups, these cell functions were greater with omega-3-supplemented diets than those for the other 2 groups. However, the flaxseed-supplemented diet contained twice as much LA and 2.5 times as much omega-3 fatty acid, entirely as ALA, compared with the EPA plus DHA content of the fish oil diet. Consequently, a much higher dietary amount of ALA was necessary to achieve neutrophil responses that were similar in some ways but dissimilar with respect to less production of proinflammatory leukotrienes with those of the fish oil diet, even though the ratio of total omega-6 to total omega-3 content was nearly identical. Given the oxidative instability of the omega-3 fatty acids in general, use of smaller amounts of fish oil to help blunt the inflammatory response is likely to be preferred in clinical practice. Finally, this study also clearly revealed that the ratio of total omega-6 to total omega-3 content of the diet is not completely reliable for use in predicting inflammatory cellular responses because different types of fatty acids cause different effects. It is likely that lower conversion rates of ALA to EPA explain this difference.

Subsequent to these studies, our laboratory group collaborated with other investigators to help design diets that contained varying amounts of fish oil to investigate the effects in 24 dogs with osteoarthritis. In that study,<sup>c</sup> affected dogs were randomly selected to receive a fish oil supplement or a control oil supplement. The amount of fish oil used was determined by use of predictive equations of fish oil enrichment as a function of dietary amounts.<sup>19</sup> Dogs were fed the respective diet for 63 days, and plasma and synovial fluid were obtained and analyzed.<sup>c</sup> The fish oil diet resulted in significant increases in EPA and DHA content in plasma and synovial fluid, with a concomitant reduction of arachidonic acid. Significant reductions in activities of matrix metalloproteinase-2 and -9, which contribute to cartilage destruction, as well as a significant increase in tissue inhibitor of metalloproteinase-2 were found. Furthermore, bicyclo-PGE<sub>2</sub>, a biomarker of inflammation, was significantly reduced in synovial fluid of dogs fed the fish oil-supplemented diet. Of additional interest is the fact that in another study,<sup>20</sup> synovial fluid concentration of PGE<sub>2</sub> was positively correlated with clinical variables of pain in dogs with osteoarthritis, which further supported the physiologic importance of the findings in the study.

### **Neurologic Development in Puppies**

In addition to the studies on canine neutrophil response to omega-3 fatty acids, our laboratory group has

been engaged in studies on effects relating to development of puppies and neurologic assessment via measurement of retinal function.

**Incorporation of ALA and DHA into canine milk**—Certain omega-3 fatty acids, specifically DHA, appear to be necessary for neurologic development.<sup>21</sup> To test this theory, diets that varied only in the type and amount of PUFA were fed to female dogs as the sole nutritional source beginning during estrus and continuing throughout breeding, gestation, and lactation. Puppies were weaned onto the same diets. Diets contained low amounts of n-3 fatty acids, moderate amounts of fish oil, high amounts of fish oil, or high amounts of ALA n-3 fatty acids from flaxseed oil. During lactation, the puppies obtained their nutrients exclusively from the milk supplied by their dams. Puppies were weaned onto the same diets fed to their respective dams. Plasma concentrations of phospholipid fatty acids during gestation and lactation reflected the diets fed, and dose responses for n-3 fatty acids were evident.<sup>22</sup> However, dogs fed the diet high in flaxseed oil did not have an accumulation of DHA, despite an increase in EPA and DPA content. This was similar to results reported for nonparous adult dogs fed ALA.<sup>5</sup>

Analysis of the patterns of fatty acids in milk samples obtained from dogs fed the diet high in flaxseed oil revealed enrichment in ALA, but no EPA or DHA.<sup>23</sup> Thus, we were able to investigate whether puppies suckling this ALA-rich milk accumulated plasma DHA, thereby suggesting its synthesis. Evaluation of the plasma phospholipid fraction of puppies during suckling revealed the expected ALA and EPA enrichment, but DHA content was also increased, compared with amounts in dogs fed a control diet. However, DHA content decreased after weaning, whereas ALA and EPA content remained high.<sup>24,25</sup> This latter finding is similar to that reported for adult dogs.<sup>5</sup> Thus, neonatal dogs appear to preferentially synthesize DHA from ALA at a time of life when demand for this fatty acid is especially high (ie, during suckling), but only for a short time. Again, it is important to mention that the milk from the dogs fed the diet high in flaxseed oil was markedly enriched in ALA because of the high dietary amounts of ALA fed, compared with results for the diets more modestly enriched with omega-3 fatty acids for the fish oil groups. It is not known whether lower amounts of ALA in the milk would support similar conversion of DHA. Hence, the efficiency of including dietary DHA from fish oil for neonatal development is preferred to feeding ALA for practical reasons as well as because of the overall improvement of retinal development and response in puppies.

**Retinal function in puppies raised on diets supplemented with fish oil**—Electroretinograms obtained from puppies (12 weeks old) of the aforementioned study<sup>22</sup> after weaning revealed a significant improvement in visual performance for those in the high-fish oil group, with a superior rod response (response strength). In addition, shorter overall response times, an improvement in response to dim light, and greater neural cascade activation were detected in the high fish

Table 1—Mean electroretinographic responses of 12-week-old puppies fed diets that varied in type of fatty acid.

Diet	Response strength ( $\mu\text{V}$ )	Response time (ms)	Extent of neural cascade activation ( $\mu\text{V}$ [ms $\times$ relative intensity])	Dim light response (relative intensity)
Low n-3 fatty acids	31.6 <sup>a</sup>	6.1 <sup>a</sup>	1.8 <sup>a</sup>	6.2 <sup>a</sup>
Moderate fish oil	24.6 <sup>a</sup>	5.6 <sup>a,b</sup>	1.6 <sup>a</sup>	5.8 <sup>a,b</sup>
High fish oil	49.5 <sup>b</sup>	4.4 <sup>b</sup>	2.5 <sup>b</sup>	5.3 <sup>b</sup>
High flaxseed oil	43.5 <sup>b</sup>	5.0 <sup>a,b</sup>	1.9 <sup>a,b</sup>	5.9 <sup>a</sup>

<sup>a,b</sup>Within a column, values with different superscript letters differ significantly ( $P < 0.05$ ). (Adapted from Heinemann KM, Waldron MK, Bigley KE, et al. 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;135:1960–1966. Reprinted with permission.)

oil group (Table 1).<sup>25</sup> Puppies in the high-flaxseed oil group had some improvement, but not to the same extent as for the puppies in the high-fish oil group. In addition, improvement was detected at a markedly high concentration of ALA, compared with results for considerably lower amounts of fish oil.<sup>25</sup> Thus, feeding preformed dietary n-3 long-chain PUFAs, compared with feeding ALA, is a more effective means of enriching DHA content of maternal plasma, which results in improved visual performance of puppies. Providing preformed long-chain n-3 fatty acids in the diet as a means of enriching plasma appears to be conditionally essential, especially for growth, development, and reproduction, because slow and inefficient conversion of ALA to DHA may not be sufficient among all dogs during these life stages.

### Clinical Summary

Progress has been made during the past years in several areas of fatty acid metabolism and nutrition for dogs. Renal and cardiovascular diseases may be amenable to dietary management with omega-3 fatty acids. Dietary changes to cause improvements in skin and coat exist, and although related to total dietary fat content, additional benefits can be derived when these diets contain higher amounts of polyunsaturated fats. The addition of ALA to a diet containing LA results in further accumulation of LA in plasma, which may contribute to a sparing effect on LA. This phenomenon may indirectly promote skin and coat benefits.

The long-chain omega-3 fatty acid, EPA, can be synthesized from ALA contained in dietary vegetable sources, and high dietary amounts of ALA can contribute to modification of cellular responses. However, because of inefficient conversion rates from ALA, the provision of preformed sources of dietary EPA appears to more efficiently modify inflammatory responses evident in dogs with osteoarthritis or other conditions related to immune function.

It is important to have adequate amounts of DHA for neurologic development, but the conversion of ALA to DHA appears to be less efficient than the conversion of ALA to EPA. However, puppies that suckle ALA-rich milk appear to accumulate DHA in their plasma for a short time prior to weaning. Nonetheless,

provision of DHA directly as fish oil during gestation and lactation (to the dams) and after weaning (to the puppies) results in improved electroretinographic responses, compared with responses to markedly higher amounts of its precursor, ALA, as well as to diets with low dietary content of omega-3 fatty acids. Thus, provision of preformed DHA in diets is more efficient for the support of the developing nervous system in puppies.

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