The role of dietary omega-3 and omega-6 essential fatty acids in the nutrition of dogs and cats: A review

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TITOLO

Il ruolo degli acidi grassi essenziali omega-3 e omega-6 nell'alimentazione del cane e del gatto: una rassegna

KEY WORDS
Dog, cat, essential fatty acids, omega-3, omega-6

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Cane, gatto, acidi grassi essenziali, omega-3, omega-6

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Summary
Omega-3 and omega-6 fatty acids are essential in all mammalians for normal growth and prevention of several diseases. Because of the seed oil production tendencies and the feeding techniques of farm animals, in the Western countries, diets for humans as well as homemade diets for dogs and cats are usually very high in omega-6 and low in omega-3 fatty acids. Several studies have shown that an optimal omega-6/omega-3 fatty acid ratio (about 6 to 1) in the diet of dogs and cats may reduce the incidence of some diseases, such as cancer and sudden cardiac death. Furthermore, the use of fatty acid supplements has proved to be beneficial in the treatment of several pathogenic conditions, such as chronic inflammatory diseases, atopy, chronic renal insufficiency, and some types of cancer. Therefore, particular attention should be paid to the type and quantity of fat sources that are used when diets for dogs and cats are formulated, in order to assure the optimal amount and balance of omega-3 and omega-6 fatty acids in the food.

Riassunto
L'apporto alimentare di acidi grassi della serie omega-3 e omega-6 è essenziale nei mammiferi al fine di assicurarne il corretto accrescimento e ridurre l'incidenza di alcune patologie. A causa delle odierne tendenze produttive nel settore delle piante oleaginose e delle moderne tecniche di alimentazione degli animali da reddito, nei paesi occidentali, le diete dell'uomo, così come quelle preparate in casa per cani e gatti, sono generalmente ricche di acidi grassi omega-6 e povere di omega-3. Numerose ricerche hanno dimostrato che un rapporto ottimale tra acidi grassi omega-6 e omega-3 (intorno a 6 a 1) nella dieta di cani e gatti può ridurre l'incidenza di alcune patologie, quali alcuni tumori e la morte cardiaca improvvisa. Inoltre, l'impiego di supplementi alimentari contenenti acidi grassi essenziali può risultare di aiuto nel trattamento di diverse condizioni patologiche, quali malattie infiammatorie a decorso cronico, atopia, insufficienza renale cronica ed alcuni tipi di tumore. È pertanto molto importante tenere conto del tipo e della quantità delle fonti lipidiche che si impiegano nella formulazione delle diete di cani e gatti, al fine di assicurare la giusta quantità ed il corretto rapporto di acidi grassi essenziali nell'alimento.

Introduction

Over the past 30 years, many studies have been conducted to investigate the metabolism of polyunsaturated fatty acids (PUFA) in humans and animals. Today, it is well known that both omega-3 and omega-6 fatty acids are essential in mammalians for normal growth and prevention of several diseases, such as cardiovascular diseases, diabetes, hypertension, chronic inflammatory and autoimmune disorders, and cancer.

The recommendations to increase omega-6 fatty acids uptake to reduce plasma concentration of cholesterol in humans have strongly influenced seed oil production and feeding techniques of farm animals. The large use of grains and oils rich in omega-6 fatty acids as feedstuffs for farm animals has led to the production of meat and eggs rich in omega-6 and poor in omega-3 fatty acids. Furthermore, modern aquaculture produces fish containing less omega-3 fatty acids than wild fish (1). As a consequence, diets for humans as well as homemade diets for dogs and cats are very likely to be high in omega-6 and low in omega-3 fatty acids.

The metabolism of omega-3 and omega-6 essential fatty acids

The omega-3 and omega-6 families consist of several fatty acids derived from two precursors, linoleic acid (LA, C18:2 n-6) and α-linolenic acid (LNA, C18:3 n-3). These two fatty acids can not be synthesized by animals and must be obtained from the diet. Once ingested, LA and LNA undergo the action of two enzymic systems, known as desaturase and elongase, and are metabolised in other acids of the same series. The desaturases act by replacing a saturated bond with a double one, the elongases exert their action adding carbon atoms to the acid in order to extend the chain. The metabolic pathway of the omega-3 and omega-6 fatty acids is shown in figure 1.

Omega-3 and omega-6 fatty acids compete for the same desaturase enzymes (2). As a result, the proportions of omega-6 and omega-3

Figure 1 - Metabolic pathway of the omega-3 and omega-6 fatty acids

Omega-6 fatty acids	Omega-3 fatty acids
18:2 (linoleic a.)	18:3 (α-linolenic a.)
↓ Δ15-desaturase	↓ Δ 6-desaturase
18:3 (γ-linolenic a.)	18:4
↓ Δ5-desaturase	↓ Elongase
20:3 (dihomo-γ-linolenic a.)	20:4
↓ Δ 5-desaturase	↓ Δ 5-desaturase
20:4 (AA)	20:5 (EPA)
↓ Elongase	↓ Elongase
22:4	22:5
↓ Elongase	↓ Elongase
24:4	24:5
↓ Δ 4-desaturase	↓ Δ 6-desaturase
24:5	24:6
↓ β-oxidation	↓ β-oxidation
22:5	22:6 (DHA)

AA = arachidonic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid

fatty acids that are available to these enzymes directly affect the quantity and proportions of arachidonic acid (AA, C20:4 n-6), eicosapentaenoic (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3) that are formed.
Like other obligate carnivores, cats show only little d-6 desaturase activity and require foods of animal origin as a source of AA, EPA and DHA (3). Conversely, dogs are able to convert LA and LNA to the long-chain PUFA by desaturase and elongase systems (4, 5).

The biological role of omega-3 and omega-6 fatty acids

Long chain PUFA can have both a functional and a structural role.
Arachidonic acid is found in fairly high proportions in the membranes of most cells, where it is bound as a component of phospholipids. Upon cellular stimulation AA is released and becomes the substrate for the synthesis of eicosanoids. Eicosanoids are polyunsaturated metabolites of fatty acids which include prostaglandins, thromboxanes, leukotrienes, and hydroxylated eicosatetraenoic acids (lipoxins).
DHA is an essential component of cell membranes. DHA is particularly present in the phospholipids of retina, cerebral synaptosomes, and sodium intra-membranous channels (6). DHA seems to play a very important role in:

1) brain development and growth
2) reproductive apparatus development and growth
3) retinal tissue development and growth

EPA is mainly a precursor of eicosanoids. When the diet is rich in omega-6 and poor in omega-3 fatty acids, eicosanoids are mainly produced from AA, but when animals ingest enough omega-3 fatty acids, EPA and DHA partially replace the omega-6 fatty acids (especially AA) in cell membranes. When the cell is injured, EPA and AA are released from the membrane by a phospholipase and metabolised to eicosanoids by two main enzymatic systems, ciclooxigenase and lipoxygenase. The metabolic pathways for the production of eicosanoids from AA and EPA are shown in figure 2.
Eicosanoids that are derived from AA are pro-inflammatory and proaggregatory, and act as potent mediators of inflammation in type I hypersensitivity reactions. Eicosanoids from EPA are less inflammatory, vasodilatory, anti-aggregatory, and prevent cardiac arrhythmia (6). These actions resist those produced by the eicosanoids from AA. The main actions of EPA and AA are summarized in table 1.
Dihomo-γ-linolenic acid (DGLA, C20:3 n-6) is produced through elongation from γ-linolenic acid (GLA, C18:3 n-6). The eicosanoids (group 1 prostaglandins and group 3 leukotrienes) that derive from DGLA suppress the synthesis of tumor necrosis factor-a which is a strong proinflammatory cytokine.

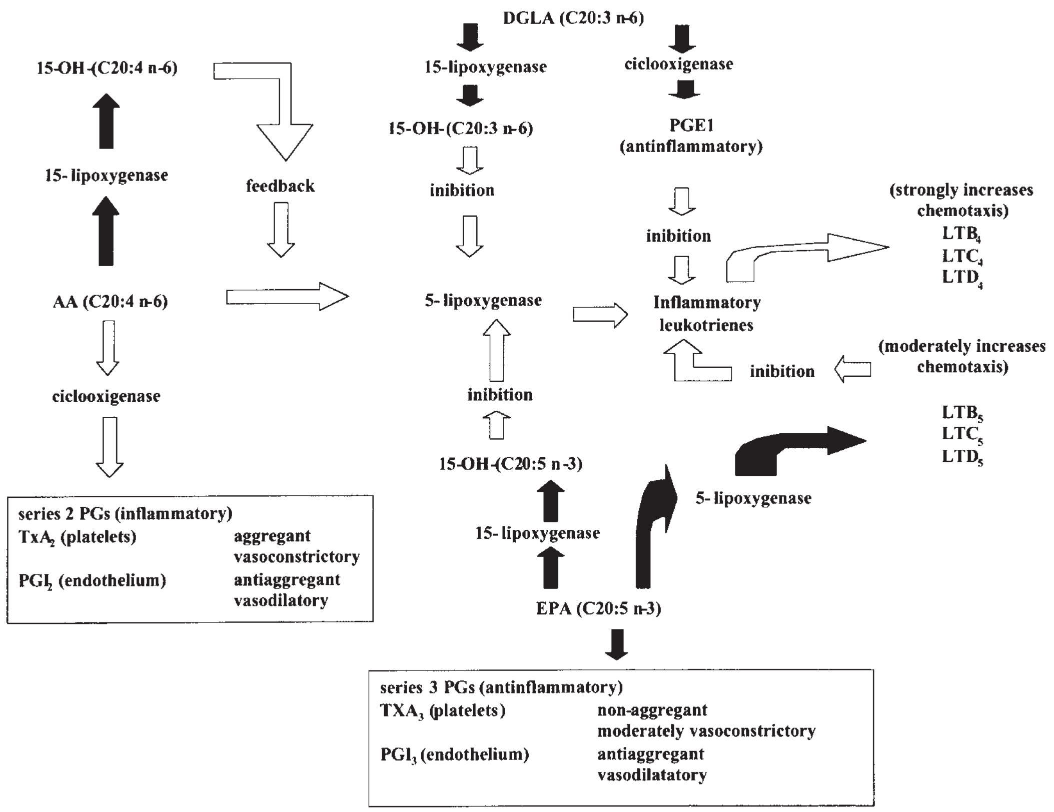
Dietary sources of PUFA

Omega-6 fatty acids are widely distributed in food of vegetable and animal origin. Most oils consumed in the Western countries (particularly corn, peanut, and sunflower oil) are very rich in LA and contain only little LNA. Among vegetable oils, flaxseed oil is the one showing the highest content in LNA; significant amounts of LNA are present also in rapeseed and soybean oil, and in walnuts. A major source of EPA and DHA is oily fish, such as sardine, salmon, mackerel, and fresh tuna. The fatty acid composition of some foodstuffs is reported in table 2.

Deficiency of PUFA in dogs and cats

Deficiencies of PUFA are not very common in dogs and cats. Commercial diets usually contain adequate PUFA; nevertheless, products that contain significant amounts of PUFA must be protected from oxidation with the inclusion of natural or synthetic antioxidants and avoiding all the factors that may activate lipids oxidation during production and storage, such as light, high temperature, and humidity. Deficiencies of PUFA may

Figure 2 - Metabolic pathways for the production of eicosanoids from AA and EPA



AA = arachidonic acid; EPA = eicosapentaenoic acid; DGLA = Dihomo-g-linolenic acid

occur when animals are fed for a prolonged time inadequate home-made diets or diets that have undergone oxidation of lipids.

A PUFA deficiency in dogs is characterized by dull dry hair, hair loss, and skin lesions (7). Hansen and Wiese (8) reported cases of external otitis in PUFA-deficient dogs.

Because of their inability to convert LA into AA (as well as LNA into EPA and DHA), cats are more likely to develop a PUFA deficiency. When cats are fed a diet lacking LA, they show signs of deficiency, such as poor growth, skin lesions, increased loss of water through the skin, reduced platelet aggregation, reproductive failure, and fatty liver. These signs of deficiency may be prevented by including LA into the diet. Nevertheless, cats fed diets containing adequate LA but lacking AA showed reproductive failure and impaired platelet aggregation (9-11). Interestingly, male cats fed LA-adequate AA-deficient diets show normal reproduction functions. This finding suggests that some conversion of LA into AA may take place (11). The existence of some δ-6 desaturase activity in cats was later confirmed by Pawlosky et al. (12).

In rats, δ-6 desaturase activity in the liver decreases at a rate propor-

Table 1 - Main actions of arachidonic and eicosapentaenoic acid (EPA)

Arachidonic acid	Effect	EPA	Effect
↑ PGE_2	↑ Platelet aggregation	↑ PGI_3	↓ Platelet aggregation, ↑ vasodilation
↑ LTB_4	↑ Inflammation	↑ LTB_5	↓ Inflammation
↑ TXA_2	↑ Platelet aggregation, ↑ vasoconstriction	↑ TXA_3	↓ Platelet aggregation ↓ vasoconstriction
↑ TNF-α	↑ Inflammation	↑ IL-2b	
↑ IL-1β	↑ Inflammation	↑ Nitric Oxide	↑ Vasodilation
↑ PAF	↑ Platelet aggregation		

PAF = Platelet activating factor

tional to the animal age (13). Even if there are no specific studies in the dog, it seems reasonable that also in old dogs the liver δ-6 desaturase activity may be lower and, as a consequence, the conversion of LA and LNA to their derivatives may be decreased. Therefore, adding a source of AA, EPA and DHA to the diet of old dogs may be helpful in preventing a deficiency of these PUFA.

Excessive intake of PUFA in dogs and cats

Cases of vitamin E deficiency in cats receiving diets very high in PUFA have been reported. Diets with a very high fish content may cause steatitis ("yellow fat disease") in cats if they are deficient in vitamin E (14, 15). Momoi et al. (16) observed that healthy cats receiving a raw fish diet had a significant increase of plasma lipid peroxide level. When a cat diet is very rich in PUFA, the NRC (17) suggests a 3-4 fold increase of vitamin E inclusion in the food. Feeding dogs with a diet with a very low omega-6/omega-3 fatty acid ratio (1.6:1) reduced plasma concentration of α-tocopherol and increased lipid peroxidation (18).

The role of PUFA in the development of the nervous system of dogs and cats

The mammalian brain is very rich in PUFA, especially DHA and AA (19). In the retina, the rod outer segment membranes of the photoreceptors are very rich in DHA (20). Essential fatty acid deficiency during early brain development may produce permanent and deleterious effects (21). Therefore, adequate PUFA dietary levels in the mother are very important both during foetal and early postnatal period. Ward et al (20) observed that dietary supplementation with different levels of DHA and/or AA in neonatal rats increased deposition of PUFA in the brain but also affected tissue levels of the other acid.

In dogs, the retinal tissue is able to synthesize DHA from docosapentaenoic acid (DPA, C22:5 n-3) which can be obtained from LNA (4). However, because the quantity of LNA that is needed to optimise neural tissue development is not known, feeding bitches and puppies with a source of dietary DHA is the best approach to provide the puppies with this nutrient.

In cats, brain DHA levels increase during the last weeks of pregnancy

Table 2 - Fatty acid composition of some foodstuffs (g per 100 g of edible portion)*

Foodstuff	Total Fat	Saturated FA	Monouns. FA	Polyunsaturated FA C18:2	C18:3	C20:4	C20:5	C22:6	TOT
Beef, rib	6.1	2.03	1.99	0.57	0.11	0.16	0.14	0.07	1.21
Chicken, breast	0.9	0.29	0.23	0.11	0	0.07	0	0.02	0.25
Lamb, leg	2.5	1.01	0.86	0.24	0.01	0.09	0	0	0.35
Pork, loin	7.0	2.23	2.38	1.68	0	0.03	0	0	1.82
Mackerel	11.1	2.61	4.13	0.16	0.15	0.16	0.73	1.26	2.46
Salmon, fresh	12.0	2.97	4.60	0.15	0.09	0.05	0.89	1.19	3.05
Sardine	15.4	4.71	2.89	0.18	0.69	1.05	1.73	2.35	6.29
Tuna, fresh	8.1	3.35	1.51	0.15	0.09	tr.	0.80	2.15	3.20
Egg, whole	8.7	3.17	2.58	1.06	0.04	0.16	0	0	1.26
Butter	83.4	48.78	23.72	1.57	1.18	0	0	0	2.75
Margarine	84.0	26.43	36.78	16.62	1.02	0	0	0	17.64
Corn oil	99.9	14.96	30.66	49.83	0.60	0	0	0	50.43
Flaxseed oil	99.9	9.40	20.20	12.70	53.30	0	0	0	66.00
Olive oil	99.9	16.16	74.45	7.85	0.99	0	0	0	8.84
Peanut oil	99.9	19.39	52.52	27.87	0	0	0	0	27.87
Rapeseed oil	99.9	6.31	61.52	20.54	9.08	0	0	0	29.62
Soybean oil	99.9	14.02	22.76	51.36	7.60	0	0	0	58.96
Sunflower oil	99.9	11.24	33.37	49.89	0.33	0	0	0	50.22
Walnuts	68.1	5.57	9.54	34.02	6.64	0	0	0	40.66

*Data from Marletta L, Carnovale E: Composizione degli alimenti. Aggiornamento 2000. Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione. 2000. CDROM.
FA = fatty acids

and keep increasing during early life. Sources of DHA and AA must be present in the diet of the queen to assure the correct development of brain and retina of the kittens (22).

The influence of PUFA on the immune system of dogs and cats

As previously mentioned, dietary lipids may modulate the immune system influencing eicosanoids production. Kearns et al. (23) showed that, despite the antiinflammatory properties of omega-3 PUFA, reducing the omega-6/omega-3 fatty acid ratio in the diet of dogs to 5:1 did not negatively affect the immune function of old animals and had some positive effect on the immune system of young animals. Feeding dogs with a diet rich in fish oil reduced the production of leukotriene B_4, a strong proinflammatory eicosanoid derived from AA, by neutrophiles (24, 25). In another study (26), when dogs were fed a diet with an omega-6/omega-3 fatty acid ratio of 1.4:1, CD4+ T lymphocyte count after vaccination was lower than in control animals, showing that a very low omega-6/omega-3 fatty acid ratio reduced immune response to vaccination. A diet with an omega-6/omega-3 fatty acid ratio of 1.4:1 reduced cell-mediated immune response and PGE_2 production in aged dogs (18).

Because of the antiinflammatory properties of the omega-3 PUFA, many studies have been conducted in animals and humans to investigate the influence of dietary PUFA on chronic diseases, such as arthrosis, dermatitis, and autoimmune diseases.
In human patients with rheumatoid arthritis, clinical improvement is achieved with the consumption of fish oil (27). Simopoulos (28) has reviewed the beneficial effects of omega-3 PUFA in human patients with inflammatory and autoimmune diseases.
In dogs with experimental and infectious arthritis, leukotriene B_4 is increased in synovial fluid (29, 30), as it is in human patients with rheumatoid arthritis (31). The reduction of the omega-6/omega-3 acid ratio in the diet of dogs with osteoarthrosis of the elbow joint did not reduce lameness during a 12 week study (32). At the present time, considering the lack of literature, it is not possible to assess the effects of dietary omega-3 PUFA on chronic arthritis of dogs and cats.
In dogs, omega-3 PUFA have been successfully used to treat a claw disorder called symmetrical lupoid onychodystrophy, usually characterised by pain and lameness (33, 34).
The role of PUFA in the treatment of allergic dermatitis in dogs and cats will be discussed in the next paragraph.

The role of PUFA in the treatment of atopy in dogs and cats

Many studies have investigated the efficacy of PUFA in the management of canine and feline atopy (allergic inhalant dermatitis). It has been estimated that 10-15% of the canine population is affected by atopy (35). Other types of allergies that may be responsible for an allergic dermatitis are flea bites and food ingredients. The main clinical sign of allergic dermatitis is pruritus with secondary skin lesions mainly resulting from self-trauma. Depending on the presence of the responsible allergens, pruritus may or may not be seasonal. Otitis externa is noted in about 55% of the dogs with atopic dermatitis (36).
Scott et al. (37) observed that a commercial diet with an omega-6/omega-3 fatty acid ratio of 5.5:1 reduced pruritus in almost 50% of the atopic dogs used for the trial. The favourable response was observed after 7 to 21 days on the diet, and was lost 3 to 14 days after the diet was withdrawn. During another study with atopic dogs, Harvey (38) observed that skin condition was improved in animals receiving a combination of fish oil (rich in EPA and DHA) and borage seed oil (rich in GLA) compared to the control animals receiving olive oil as a placebo. During another study, skin condition improvement was observed in 19 of 26 atopic dogs receiving a mixture of fish oil and evening primrose oil (also rich in GLA; 39). Another source of GLA is blackcurrant seed oil. When fed to atopic dogs, blackcurrant seed oil reduced pruritus, erythema and skin lesions (40).
Conversely, other researchers did not notice any significant benefits from feeding fish oil and evening primrose oil to atopic dogs (41, 42). In another trial (43), changing the dose of omega-3 PUFA and the omega-6/omega-3 ratio did not produce any benefit on clinical signs in dogs with pruritus.
In cats with crusting dermatosis, Harvey (44) observed that a mixture of evening primrose oil and fish oil was more effective than fish oil alone in improving skin condition. During a precedent study (45), six of eight cats with pruritus showed some benefit from dietary supplementation with PUFA. Feeding an omega-3 fatty acid supplement to non-pruritic cats with miliary dermatitis lead to the complete disappearance of clinical signs in three animals of five (46). Conversely, in another study, feeding primrose oil to 15 pruritic cats did not improve their skin condition (47). When used together with an antihistamine, an omega-3/omega-6 fatty acid supplement was effective in reducing pruritus in 6 cats of 11 (48). Interestingly, no benefit was observed when the antihistamine or the fatty acid supplement

were used alone, suggesting a synergistic action of the two antiinflammatory agents tested.

The lack of clear benefits from feeding PUFA to dogs and cats with dermatitis and the sometimes controversial results obtained may be due to different causes, such as inadequate duration of treatment, lack of a control diet, different composition of diets and supplements used in the experiments, different doses of PUFA fed to the animals, and different etiology of disease.

Cardiovascular effects of PUFA in dogs

The beneficial effects of omega-3 fatty acids on coronary heart disease have been shown in hundreds of experiments in animals and humans (49). Dietary omega-3 fatty acids prevent heart disease through several actions, such as prevention of arrhythmias, production of prostaglandins and leukotrienes with antiinflammatory properties and inhibition of the synthesis of cytokines and mitogens that augment inflammation, stimulation of nitric oxide release, antithrombotic properties, reduction of plasmatic triacylglycerols and VLDL, and inhibition of atherosclerosis (50).

Despite the fact that atherosclerosis is not a major clinical problem in dogs and cats, it is known that sled dogs like trained human athletes may develop pathological alterations of the heart conduction system (fibrosis and fat infiltration) that can eventually lead to sudden death (51). Billman et al. (52, 53) showed that omega-3 PUFA have antiarrhythmic effects also in dogs and can prevent sudden cardiac death. Kang and Leaf (54) observed that omega-3 PUFA stabilize electrically every myocyte in the heart of dogs by increasing by approximately 50% the electrical stimulus required to elicit an action potential and prolonging the relative refractory time by approximately 150%.

Freeman et al. (55) showed that fish oil supplementation can improve the health status of dogs with heart failure, reducing Interleukin-1β (IL1) production and improving the cachexia that is often associated with heart failure. IL1 is correlated with higher mortality rates and this may be the consequence of the negative inotropic effect of IL1 or of the fact that IL1 increases skeletal muscle protein turnover and reduces cardiac myocyte protein synthesis (56).

The role of PUFA in the treatment of chronic renal disease in dogs and cats

Despite the fact that renal disease is a very common cause of death in dogs and cats, the causes of renal disease and its progression are only poorly understood. In dogs and cats with renal insufficiency, glomerular hypertension and hypertrophy are observed (57, 58). These findings are supposed to represent the adaptive renal response to the injury. Frequently, renal failure with glomerular hypertension is associated with elevation of systemic arterial pressure of dogs and cats (59, 60). In dogs with renal failure, preglomerular vessels are dilated and even transient elevations of systemic pressure are transmitted to the susceptible glomerular capillary bed causing further progression of the disease (61).

Intrarenal hemodynamics are influenced by vasoactive renal eicosanoids, such as Prostaglandin E_2 and I_2 and Thromboxane A_2 (62, 63), both deriving from AA. While PGE_2 and PGI_2 are powerful vasodilators and help maintain renal blood flow and glomerular filtration, TXA_2 reduces renal blood flow and glomerular filtration and induces aggregation of platelets (64). Intrarenal platelet aggregation may lead to proteinuria due to higher capillary permeability and to intraglomerular coagulation with subsequent fibrosis and sclerosis (65). Conversely, TXA_3, which is derived from EPA, does not cause platelet aggregation (66).

Brown et al. (67) fed dogs with renal insufficiency different sources of fat. Feeding the animals with safflower oil (rich in omega-6 fatty acids) enhanced renal injury while feeding fish oil prevented deterioration of renal function. Dietary supplementation with beef tallow (a source of saturated fatty acids) also produced a progressive decrement of renal function but the rate of function decline was slower than in animals receiving safflower oil. During another study (68), dogs with early renal insufficiency were fed safflower oil, fish oil or beef tallow. Compared to feeding beef tallow, feeding fish oil decreased serum cholesterol concentration and PGE_2 and TXA_2 excretion, while dietary supplementation with safflower oil increased eicosanoids excretion, glomerular capillary pressure and glomerular enlargement.

The role of PUFA in the prevention and treatment of neoplastic disorders in dogs and cats

In humans, there is evidence that omega-3 fatty acids may have some beneficial effect on some neoplastic diseases, such as breast, colorectal, and prostatic cancer, preventing development and growth of tumors and reducing the incidence of metastatic disease (69-72).

Cachexia is a very common consequence of malignancy and it is caused by a number of derangements in carbohydrate, lipid and protein metabolism that are observed in humans (73, 74) as well as in dogs (75, 76). Since TNF and interleukin-6 are supposed to play a role in the pathogenesis of cancer cachexia (77), feeding fish oil to cancer patients may reduce the production of these eicosanoids and consequently the incidence of cachexia (78, 79).

In dogs with lymphoma, dietary omega-3 fatty acids significantly increased disease free interval and survival time (80).

Conclusions

There is evidence from the literature that the omega-6/omega-3 fatty acid ratio of the diet influences growth and health status of dogs and cats. Essential fatty acids are very important for the development of the nervous system and an optimal dietary omega-6/omega-3 fatty acid ratio (about 6 to 1) reduces the incidence of some diseases, such as cancer and sudden cardiac death. Furthermore, the use of fatty acid supplements has proved to be beneficial in the treatment of several pathogenic conditions, such as chronic inflammatory diseases, atopy, chronic renal disease, and some types of cancer. Therefore, particular attention should be paid to the type and quantity of fat sources that are used when diets for dogs and cats are formulated, in order to assure the optimal amount and balance of omega-3 and omega-6 fatty acids in the food.

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