

# Effects of Dietary Lipids on Renal Function in Dogs and Cats

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## Dogs, Progressive Renal Disease, and Dietary Lipids

End-stage renal disease is a common cause of death in dogs and cats. Unfortunately, despite appropriate therapy for the primary cause of the disease, renal failure frequently is progressive, leading to terminal uremia.<sup>1,2</sup> This has at least two important consequences for a dog or cat with renal disease. First, the disease is inherently unstable and frequent reevaluations and adjustments in therapy are required. Second, because of the tremendous cost and technical difficulty associated with therapy for end-stage uremia (i.e., dialytic therapy or renal transplantation), efforts designed to slow the rate of progression of renal disease are particularly important in veterinary medicine.

The cause of progressive renal injury has been the focus of great attention in nephrology. It has long been recognized that renal disease in human beings usually progresses, even if appropriate therapy eradicates the primary cause of the renal injury. Thus, once renal injury reaches a certain threshold, secondary factors appear to be the critical determinants of progressive renal injury.

A particular model of renal disease, referred to as the remnant kidney model, has been critical in advancing our understanding of this inherent progression of renal disease. In this model, renal mass is reduced by uninephrectomy and infarction of a portion of the contralateral kidney. Following this reduction of renal mass, remaining (remnant) nephrons are initially normal and renal function is adequate to sustain only mild to moderate azotemia with no clinical signs. However, over the ensuing months, remnant renal tissue develops structural lesions and many nephrons are ultimately destroyed in this process. As more and more nephrons are destroyed, renal function declines over time. As investigators studied this model of progressive renal dis-

ease, it became apparent that a variety of adaptive changes, acting as secondary factors, were

important in the progressive nature of renal failure in animals. In particular, emphasis has been placed on possible roles for (1) glomerular hypertension, (2) intrarenal inflammation, (3) hyperlipidemia with lipid peroxidation, and (4) growth factor-induced renal injury.<sup>3-8</sup>

In the diseased kidney the surviving, or remnant, glomeruli become larger and exhibit an increase in glomerular capillary pressure, referred to as glomerular hypertension. Brenner and colleagues<sup>3</sup> proposed that glomerular hypertension was maladaptive, causing renal injury. Recently, studies have shown that, in both dogs and cats with renal insufficiency, glomerular hypertension is observed.<sup>9,10</sup>

Recently, in an experimental model of diabetic nephropathy in dogs, therapy that reduced the extent of glomerular hypertension was shown to be renoprotective.<sup>11,12</sup> Because of similarities in adaptive changes in diabetes and remnant kidney, two models of renal disease, it is reasonable to speculate that the favorable response to lowering glomerular pressure in diabetes would also be observed in other forms of chronic renal disease in dogs. If so, efforts to reduce the extent of glomerular hypertension might prove beneficial in all animals with renal failure.

Most renal diseases have an inflammatory component. While this has long been well recognized for diseases affecting the glomerulus, only recently has the importance of inflammation been recognized in chronic tubulointerstitial diseases as well. Most renal injury is characterized by infiltration and activation of inflammatory cells. Consequently, the use of therapy designed to limit the activation of inflammatory cells could interrupt the process and prevent progressive renal injury.

Abnormalities of lipid metabolism in renal disease have been characterized in human beings<sup>5</sup> and dogs<sup>13,14</sup> and generally include elevated serum levels of total cholesterol, lower density lipoproteins, and/or triglycerides. Support for an adverse effect of diets enriched with saturated fatty acids was derived from experiments in which rats were fed high calorie diets containing saturated fatty acids to induce hyperlipidemia, which led to glomerulosclerosis and progressive renal injury.<sup>5</sup>

Lipids, particularly oxidized low density lipoprotein particles, stimulate glomerular mesangial cell proliferation and production of excess mesangial matrix, a process referred to as glomerulosclerosis.<sup>5</sup> Uremic renal failure has been causally linked to hyperlipidemia in guinea pigs<sup>15</sup> and rats.<sup>16</sup>

Fatty acids are generally categorized on the basis of number and location of carbon-carbon double bonds. Dietary fatty acids that contain no double bonds, such as palmitic acid, are referred to as saturated fatty acids. Animal fats, which contain predominantly saturated fatty acids, are often incorporated into feline diets because of availability and palatability. In contrast, plant sources of fat contain high proportions of the polyunsaturated fatty acid, linoleic acid. Linoleic acid is referred to as an omega-6 polyunsaturated fatty acid (n-6 PUFA) because the first carbon-carbon double bond occurs at the sixth carbon from the methyl group. In most mammals, including people and dogs, linoleic is readily converted to arachidonic acid, the immediate precursor of eicosanoids (prostaglandins and thromboxanes). An alternative source of PUFA is menhaden fish oil derived from fish feeding on plankton. These oils are rich in eicosapentaenoic acid and docosahexaenoic acid, which are omega-3 PUFAs (n-3 PUFAs).

Thus substantially different chemical forms of fatty acids are obtained when pet foods are supplemented with lipids obtained from animal fat, plant oil, or menhaden fish oil. These dietary fatty acids may affect renal function through effects on renal eicosanoid metabolism.

Eicosanoids are compounds derived from PUFA within cell membranes and include prostaglandins, prostacyclin, and thromboxanes.<sup>17</sup> The usual precursor for eicosanoids is arachidonic acid. In dogs, people, and rats, arachidonic acid is derived from the PUFA linoleic acid, which comprises 50% to 80% of plant oils. However, cats have limited

hepatic delta-6 desaturase activity and thus cannot effectively convert linoleic to arachidonic acid and both are considered essential dietary fatty acids in cats.<sup>18</sup> It should be noted, however, that the activity of this enzyme in the feline kidney and the intrarenal capacity to convert linoleic to arachidonic acid have not been well studied.

The principal eicosanoids derived from the n-3 polyunsaturated fatty acid, arachidonic acid, include prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), and thromboxane A<sub>2</sub> (TxA<sub>2</sub>). The vasodilatory eicosanoids, PGE<sub>2</sub> and PGI<sub>2</sub>, increase renal blood flow and glomerular filtration rate (GFR). They also serve to promote, directly or indirectly, intrarenal inflammation. In contrast, renal TxA<sub>2</sub> has renal vasoconstrictor effects, with variable effects on GFR. Both thromboxanes and PGI<sub>2</sub> alter platelet function: thromboxanes enhance and PGI<sub>2</sub> inhibits platelet aggregation.

Menhaden fish oil contains n-3 PUFA, which competes with arachidonic acid in the production of eicosanoids. Consequently, animals fed menhaden fish oil have a diminution of the 2-series of eicosanoids normally derived from arachidonic acid. Importantly, the eicosanoid derivatives of n-3 PUFA are less potent than the usual arachidonic acid derivatives. In particular, thromboxanes derived from n-3 PUFA have little vasoconstrictive or platelet aggregating effect. Replacement of dietary saturated fat with PUFA will tend to lower plasma lipid concentrations.

Proponents of the importance of hemodynamic causes of progressive renal injury have proposed a link between production of the 2-series of prostaglandins and thromboxanes and progressive renal disease. This theory is based on renal micropuncture studies suggesting that glomerular hypertension is dependent on renal eicosanoids.<sup>3</sup> Manipulations that alter renal production of eicosanoids, such as dietary supplementation with menhaden fish oil, slow the progression of chronic renal disease in some studies of laboratory animals.

While diets rich in saturated fatty acids raise serum cholesterol and triglyceride concentrations in laboratory animals with renal failure, enhancing diets with PUFA lowers plasma lipid concentrations. Preliminary studies in our laboratory have established that cats and dogs with induced renal dysfunction exhibit hypercholesterolemia and/or hy-

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pertriglyceridemia. We have recently observed that the hyperlipidemia in dogs with induced chronic renal failure can be modified by changes in dietary fatty acid composition. Specifically, animals fed a diet enriched with PUFA (safflower oil or menhaden fish oil) exhibited an amelioration of the hyperlipidemia observed in dogs fed a diet containing predominantly saturated fatty acids. Previous studies in our laboratory have established an association between hyperlipidemia and progressive renal failure in dogs.<sup>14</sup> Loss of renal function in dogs with induced renal disease was directly related to plasma triglyceride and total cholesterol concentrations.

In summary, dietary n-3 PUFA supplementation might be expected to modify intrarenal hemodynamics, reduce intrarenal inflammation, limit the extent of hyperlipidemia, and reduce local generation of growth factors by inhibiting intrarenal platelet activation. As a potential therapy to slow the rate of progression of renal disease, dietary n-3 PUFA supplementation was hypothesized to exert renoprotective effects by altering the critical secondary factors involved in the progressive renal failure: glomerular hypertension, intrarenal inflammation, hyperlipidemia with lipid peroxidation, and intrarenal growth factor elaboration. Critically, long-term studies in our laboratory have shown that a diet supplemented with menhaden fish oil will preserve renal function in dogs with induced renal failure, when compared to supplementation with safflower oil (a rich source of n-6 polyunsaturated fatty acids) or a highly saturated fat source (beef tallow). While further studies are needed to understand the mechanisms responsible for this protection, the use of diets supplemented with menhaden fish oil has become an important consideration in the therapy of chronic renal disease in dogs.

### Cats, Normal Renal Function, and Dietary Lipids

We studied the effects of variations in dietary omega-3:omega-6 polyunsaturated fatty acids (PUFAs) on plasma lipoproteins, urinary eicosanoid excretion, systemic arterial pressure, and renal function. There was a significant effect of dietary fatty acid composition on plasma total lipoprotein concentrations and on plasma total

cholesterol concentration, with a lowering of both plasma concentrations observed only for the diet with the highest omega-3 content, with an omega-6:omega-3 ratio (n-6:n-3) of 1:1.

There was no apparent trend for dietary n-6:n-3 to alter urinary PGE<sub>2</sub> excretion. As dietary n-6:n-3 declined from 10:1 to 1:1, there was a nonsignificant trend for this dietary manipulation to lower renal thromboxane A<sub>2</sub> production.

The hypothesis that dietary n-3 supplementation would lower systemic arterial blood pressure was not supported by our results of average mean arterial pressure obtained by radiotelemetry in undisturbed, normal cats. There was a small trend for n-3 PUFA to lower mean blood pressure in these cats, but this was not statistically significant. This trend is similar to that observed in normal human beings given fish oil supplements. The question remains as to whether or not hypertensive cats would benefit from dietary fish oil supplementation.

Finally, the lower dietary n-6:n-3 PUFA ratio increased glomerular filtration rate in normal cats. There was no significant effect and no discernible trend for effect of dietary PUFA on proteinuria.

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### Renal Disease and Dietary Fats: Further Recommendations

In cats, dietary supplementation with n-3 PUFA had no apparent deleterious effect on lipid metabolism, immune function, blood pressure, or renal function. At higher levels of supplementation, renal function was actually increased in normal cats. These data support the assertion that this dietary maneuver is safe for normal cats and provides some encouragement for further consideration of dietary n-3 in cats with renal disease, systemic hypertension, or hypersensitivity reactions. Further studies will be required, however, to characterize the response of cats with renal disease, systemic hypertension, or hypersensitivity reactions to this dietary manipulation.

Preliminary evidence from recent studies in our laboratory suggest that a dietary trial of menhaden fish oil supplementation could be considered in dogs with renal disease. However, the n-6:n-3 ratios of the diets in our study were <0.2:1 and >50:1, ratios that are difficult to achieve in commercially available preparations. The diet

can be supplemented with PUFA. Commonly available veterinary fatty acid supplements contain a mixture of n-3 and n-6 PUFAs, a combination that has not been studied in dogs or cats with renal disease. Compared to dogs with early renal disease fed a menhaden fish oil-enriched diet, a safflower oil-enriched diet contributes to progressive renal disease.<sup>15</sup> Thus results of our studies indicate that n-6 PUFA supplements should be avoided in early renal failure. The diet can be supplemented with available products that supply only n-3 PUFA, which are commonly available at health food stores. As with any therapeutic maneuver, baseline values for serum creatinine concentration, the urine protein-to-creatinine ratio, and mean arterial pressure (if available) should be obtained prior to instituting dietary n-3 PUFA supplementation. Generally, a supplement of 0.5 to 1.0 g of n-3 PUFA/100 kcal of food is a reasonable starting dose. Based on studies in our laboratory, 2 to 4 weeks are required to see initial effects of this dietary manipulation. All parameters should be reevaluated at 2 and 4 weeks and then monthly for 6 months. Therapy with n-3 PUFA should be discontinued if no beneficial effect or an adverse effect is observed during this trial.

A key issue will be to define the ideal dietary n-6:n-3 ratio or dose of PUFA for diets for dogs with renal failure. In the interim dietary fatty acid composition in the middle of the n-6:n-3 ratio range of 0.2:1 to 5:1 may be considered a desirable goal for dogs with early renal failure. Manufacturers have begun to analyze diets and supply veterinarians with information pertaining to dietary fatty acid composition. At this time, it would be appropriate to consider a diet in this mid-range.

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