



The Impact of Dietary Fat and Polyunsaturated Fatty Acids on Renal Disease

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ABSTRACT

Modifying the diet is an important component of the medical management of chronic renal failure (CRF) in dogs. Protein, sodium, and phosphorus contents of such diets are restricted, and the level of B-complex vitamins is increased. These diets also offer a high energy density from non-protein sources and are often high in fat. A study using a commercial canned diet designed for dogs with CRF indicates that increases in total cholesterol associated with high density lipoproteins are unlikely to be atherogenic or to promote glomerulosclerosis; this suggests that using high levels of fat to increase non-protein energy is not detrimental to the CRF patient. Some eicosanoids also play an important role in renal disease; for example, supplementation with dietary fish oils has been shown to be beneficial in some animal models of renal disease. A study compared urinary eicosanoid concentrations in normal dogs to those in dogs with CRF; the impact of safflower oil or menhaden fish oil was evaluated. Safflower oil significantly increased glomerular filtration rate, which could be of short-term benefit to the patient.

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Dietary modification is an important component of the medical management of chronic renal failure (CRF) in dogs. The objectives are¹:

- to meet the patient's nutrient and energy requirements
- to alleviate clinical signs of uremia through reduction of protein catabolites
- to minimize electrolyte, vitamin, and mineral disturbances
- to slow progression of renal failure.

Diets designed to achieve these goals have a number of modifications to their nutrient profiles compared with normal foods. These may include restricted phosphorus, protein, and sodium contents, enhanced levels of B-complex vitamins, and a high energy density using nonprotein sources. A number of studies have shown that restriction of dietary protein and phosphorus can reduce azotemia and bring about clinical benefits in dogs with CRF²⁻⁶ although controversy exists regarding the level of protein restriction and at what stage such restriction may be needed.⁷ The data regarding phosphorus restriction appear more convincing.³ Specific management recommendations based on stages of disease have recently been made.⁸ Use of a diet restricted in phosphorus, but not in protein, is recommended for dogs that are azotemic but not uremic. Recommendations for uremic dogs with

more advanced disease include restriction of dietary protein in addition to phosphorus.

These aspects of nutrient profile may address the requirements to alleviate uremia, improve some aspects of mineral and endocrine imbalance and, perhaps, impact favorably on the progression of disease. The key goal of any dietary regimen, however, is to meet the nutrient and energy requirements of the patient. For these reasons, canned diets designed to support dogs with CRF tend to be high in fat, as this increases both energy density and palatability, thus helping to avoid catabolic states that would result from inadequate food intake.

LIPIDS AND RENAL DISEASE

Abnormalities in lipid metabolism have been documented in a variety of human renal diseases⁹ and have also been reported in dogs with both spontaneous and induced renal disease.^{10,11} Changes in human patients are thought to result (at least in part) from decreased activity of enzymes involved in lipoprotein metabolism—lipoprotein lipase and lecithin:cholesterol acyltransferase (LCAT, see below)—resulting in increased concentrations of potentially atherogenic lipoproteins (partially metabolized low-density and very low density lipoproteins). In addition to creating a more atherogenic environment, these lipoproteins may also be responsible for glomerulosclerosis, a process that may have similarities to atherosclerosis.^{9,12,13} Increased serum cholesterol concentration and a shift in



the distribution of cholesterol from high-density to low-density lipoprotein fractions was also noted in a small group of dogs with spontaneous renal failure.¹¹ Human patients with congenital LCAT deficiency develop hyperlipidemia and, frequently, progressive glomerular injury. Glomerular deposits resembling altered low density lipoproteins have been detected in patients with this condition.^{14,15}

In addition to these observations of lipid abnormalities in renal disease, a number of studies have evaluated the effects of hyperlipidemia on renal disease. High-cholesterol-containing diets have been shown to increase focal glomerular sclerosis in guinea pigs and rats.^{16,17} In the latter study, it was the plasma very low density lipoprotein-cholesterol that was noted to increase. Pharmacological intervention to reduce endogenous hyperlipidemia has also been shown to reduce focal glomerulosclerosis in rats.^{18,19} The extent to which these observations may apply to dogs and cats with CRF remains to be elucidated.

The effect on lipid profiles of a commercial canned diet (WALTHAM Veterinary Diet; PEDIGREE Low Phosphorus Medium Protein Diet) designed for the support of dogs with CRF has been investigated recently.²⁰⁻²² The diet, which provides approximately 57% of metabolizable energy from fat, was fed to 18 healthy dogs for 10 days and to 16 dogs with naturally occurring CRF for 21 days. Plasma total cholesterol, triglyceride, lipoprotein cholesterol distribution, and LCAT activities were investigated at the start and end of the feeding period. LCAT is involved in cholesterol metabolic regulation and associated with high density lipoproteins, the major lipid transport particle in dogs. As part of reverse cholesterol transport, it is significant in that it catalyzes the first important enzymatic step in returning cholesterol to the liver for utilization or excretion.²³

Significant ($P < 0.01$) increases in plasma total cholesterol were seen in both groups of dogs. This was associated with significant increases in α -migrating (high-density) lipoproteins in the healthy dogs; a similar trend was observed in the dogs with CRF, although the difference was not statistically significant. There were no changes in β -migrating (low-density) lipoproteins or triglyceride concentrations in either group. Plasma LCAT activity increased significantly in the healthy dogs and, again, a similar trend was seen in the dogs with CRF.

It was not possible to determine whether the abnormalities in lipoprotein metabolism known to occur in human patients with CRF (such as decreased LCAT activity) were present in the dogs because some had been switched to phosphorus- and protein-restricted, relatively high-fat diets prior to study entry. If similar abnormalities do occur in dogs with CRF, the changes observed in this study as a result of dietary intervention with the canned diet could actually benefit the patient by reversing abnormalities induced by CRF. Even if this is not the case, the

increase in total cholesterol associated with the high density lipoproteins is unlikely to be atherogenic or to promote glomerulosclerosis, indicating that inclusion of high fat levels to increase nonprotein energy in this type of diet is not going to be detrimental to the CRF patient.

EICOSANOIDS AND RENAL DISEASE

The families of prostaglandins, leukotrienes, and related compounds are termed eicosanoids because they are derived from 20-carbon polyunsaturated fatty acids (dihomo- γ -linolenic acid, arachidonic acid, or eicosapentaenoic acid [EPA]). The main classes of prostaglandins are subdivided according to the number of double bonds in their side chains, which reflects their fatty acid precursors. Thus prostaglandins derived from arachidonic acid are designated by the subscript 2 and those from EPA by the subscript 3. Prostaglandins and thromboxanes result from the initial action of cyclo-oxygenase, whereas leukotrienes result from the action of various lipoxygenases.²⁴

These compounds have extremely widespread and diverse effects, some of which may be of great importance in renal disease. The prostaglandins PGE₂ and PGI₂ help to maintain renal blood flow and glomerular filtration in clinical conditions associated with renal compromise and are generally considered to be beneficial.²⁵ PGI₃ has been reported²⁶ as having similar efficacy to PGI₂. Conversely, thromboxane A₂ (TXA₂) decreases renal blood flow and glomerular filtration.²⁵ It is also a powerful inducer of platelet aggregation. Aggregation of platelets could lead to a release of platelet products that may increase capillary permeability (contributing to proteinuria). Platelet aggregation may also cause intraglomerular coagulation with subsequent fibrosis and sclerosis.²⁷ Thromboxane A₃ (TXA₃) derived from EPA is biologically inert.²⁶ TXA₂ has a very short half-life and breaks down nonenzymatically to the stable TXB₂; it is this metabolite that is usually measured in experimental situations.

Marked increases in renal production of prostaglandins and/or TXB₂ have been reported in humans with chronic renal disease and various animal models of renal disease.²⁷⁻³¹ While increases in vasodilatory prostaglandins may be beneficial in helping to maintain renal function, absolute or relative increase in thromboxane is likely to be deleterious and may be involved in progression of disease. It has been reported recently that the ratio of PGE₂ to TXB₂ was significantly reduced in dogs with naturally occurring CRF.³² Pharmacological or dietary intervention to alter these changes in eicosanoids may provide a means for modifying the disease process.

Suppression of thromboxane synthesis with specific inhibitors has been shown to be beneficial in experimental situations. It reduced proteinuria and glomerular damage while preserving renal blood flow and glomerular filtration rate in

rats with naturally developing focal glomerular sclerosis²⁹; similar effects were seen in rats with subtotal renal ablation.²⁷

Renal eicosanoid production may also be altered by dietary means. Inclusion of fat sources rich in EPA (e.g., marine fish oils) would be expected to decrease production of dienoic prostaglandins and increase that of the trienoic series.³³ This would be expected to decrease PGE₂, PGI₂, and TXA₂; however, PGE₃ and PGI₃ are thought to be equipotent, whereas TXA₃ is biologically inert.

Dietary fish oil supplementation has been shown to be beneficial in some animal models of renal disease that involve an immune component, e.g., murine lupus.^{34–36} Marked decreases in production of dienoic eicosanoids, along with increased production of PGE₃ (although levels were much lower than those of the dienoic compounds), were noted with fish oil supplementation in one of these studies.³⁵ In contrast with these results, detrimental effects of fish oil were noted in rats with subtotal nephrectomy of varying degrees; adverse effects included increased glomerular sclerosis and accelerated death rates.²⁵

It was suggested that suppression of PGE₂ may have been deleterious and outweighed any beneficial effects of suppression of TXA₂. Presumably, any increased production of PGE₃ was inadequate to compensate for the reduction in PGE₂ in this model. It is of interest that a diet high in linoleic acid was shown to be beneficial in another subtotal nephrectomy study, although this occurred in the absence of changes in urinary excretion of dienoic eicosanoids.³⁷ Clearly, further research is necessary to evaluate better the potential for use of polyunsaturated fatty acids in naturally occurring disease in other species. In addition, most of these studies used the chosen fat source (e.g., menhaden or safflower oils) at 20%, or more, by weight of the diet; further study is also needed at more practical levels of inclusion.

Some of these issues have been addressed recently in dogs with naturally occurring CRF.^{38,39} The aims of this study were to compare urinary eicosanoid concentrations in normal dogs (n=17) and those with naturally occurring CRF (n=32) and to evaluate the impact of safflower oil (SFO) or menhaden fish oil (MFO) supplementation in dogs fed phosphorus- and protein-restricted diets (WALTHAM Veterinary Diet Canine Low Protein and Canine Medium Protein). Following a basal period, a crossover design was implemented for oil supplementation using a 3-week washout period. Compliance and oil carryover effects were monitored by serum phospholipid fatty acid analysis. TXB₂ and PGE₂ concentrations were measured in free catch urine samples by ELISA, with PGE₂ first extracted on C18 silica columns.

Decreased PGE₂ concentrations (P=0.00003) and PGE₂:TXB₂ ratios (P=0.0003) were found for dogs with CRF compared with control dogs on entry and after diet acclimation (P=0.003 PGE₂; P=0.006 PGE₂:TXB₂). Among all dogs, MFO

supplementation resulted in a decrease in PGE₂ (P=0.03). In the group of CRF dogs fed the dry diet, PGE₂ concentrations were increased (P=0.02) when the diet was supplemented with SFO. TXB₂ concentrations were variable but not significantly different in any group. Individual patient responses consistently showed PGE₂ decreased with MFO and increased with SFO. Of particular interest was the observation that SFO resulted in a significant increase in glomerular filtration rate (GFR) (P=0.03) in all CRF dogs. The increase in GFR associated with SFO supplementation was, on average, 50%.

The mechanism by which supplementation with SFO increased GFR was not determined in this study. The two mechanisms considered most likely are either an increase in the surface area for filtration, mediated through mesangial relaxation, or increased glomerular capillary pressure, mediated through changes in vascular tone. Increased GFR would be of short-term benefit to the patient as it would help to decrease accumulation of toxic metabolic waste. Further studies are required to evaluate the long-term consequences of this effect.

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