The impact of dietary fat and polyunsaturated fatty acids on chronic renal diseases

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ABSTRACT

The studies suggest an association between polyunsaturated fatty acids (PUFAs) and the development of chronic kidney disease. Study the relationship between PUFAs and renal function in older adults. Dietary modification is an important component of the medical management of chronic renal failure (CRF) in dogs. The objectives are 1: 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. People with higher creatinine clearance had higher concentrations of HDL cholesterol, total plasma PUFAs, plasma n-3 FA, and lower triglycerides. Baseline total plasma PUFAs, n-3 FA, n-6 FA, and linoleic, linolenic, and arachidonic acids were strong independent predictors of less steep decline in creatinine clearance from baseline, after adjusting for baseline creatinine clearance). After adjusting for baseline creatinine, baseline total plasma PUFAs, n-3 FA, and linoleic, linolenic, and arachidonic acids were negatively associated with creatinine at 3-year follow-up. People with higher plasma PUFAs at enrollment had a lower risk of developing renal insufficiency.

INTRODUCTION

An intense interest in the health benefits of polyunsaturated fatty acids (PUFAs). These PUFAs have several benefits on cardiovascular disorders (CVD), autoimmune, inflammatory diseases and cancer. The beneficial effects of PUFA are attributed to eicosanoid synthesis such as prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs). The importance of these FAs to infant nutrition is particularly relevant because DHA is important for fetal and term-infant neural development. Although PUFA can be synthesized in the body by elongation and desaturation of α-linolenic acid (ALA), ingestion of the preformed molecules usually is more effective, especially for the very young or the elderly. Changes in the composition of PUFA in diet may modify glomerular hemodynamics in normal rats and affect the chronic course of renal disease in partially nephrectomized rats. Thus, dietary PUFA supplementation might alter progressive canine nephropathies. The hypothesis that dietary PUFA supplementation may delay the progression of chronic renal insufficiency in dogs. In particular, diets supplemented with n-6 PUFA exhibited severe glomerular hypertension associated with rapidly progressive renal failure. The dietary supplementation with n-3 PUFA prevented deterioration of the glomerular filtration rate and preserved renal structure. The dietary PUFA supplementation may alter renal hemodynamics and the long-term course of renal injury. The patients on PUFA, the rate of rise of creatinine was slower and
there was improvement in proteinuria and serum albumin levels. There was reduction in serum triglyceride and cholesterol levels. The role of PUFA in prevention of progression of chronic renal disease is not conclusive and may need larger controlled studies. Positive effect of PUFA is in retardation of the progression of chronic renal disease (CRD). PUFA are beneficial on the lipid and immune abnormalities secondary to chronic renal failure (CRF) and may have a useful effect on progression of CRF. The effect of PUFA on progression of CRD, lipid metabolism and proteinuria. Patients with established diabetic or nondiabetic chronic renal disease, patients with Serum creatinine > 6 mg% and comorbid conditions such as chronic liver disease, chronic infections and protein malnutrition were excluded. The role of PUFA in prevention of progression of CRD is not conclusive and may need larger controlled studies.

The sources of PUFA are marine mammals and vegetables like soyabean, butternuts and common beans. It has also been suggested that EPA plays a protective role in the progression of chronic renal failure (CRF). However, these findings are controversial since multifactorial mechanisms appear to be involved in its pathogenesis. Besides inflammatory responses, altered PG synthesis, coagulation abnormalities, and alterations in lipid metabolism observed in some models of CRF, the hemodynamic changes, such as increased glomerular pressure and flow are also important for progression of CRF. It has been proven that PUFA can prevent or slow down the decline in renal function in a variety of animal models of renal disease. In various studies, a positive effect of the use of linoleic acid (LA) on renal function had been described. However, this was not the case in all animal models studied. A more consistent pattern with positive effects could be found with the use of \( \omega-3 \) PUFA mixtures, although one study had only reported unfavorable findings. Up to now, studies on the effect of fish oil on renal function in patients with chronic renal insufficiency are relatively rare. Glomerular filtration rate increased, there was rise in effective renal plasma flow and a fall in filtration fraction. There was a tendency for proteinuria to fall. These changes suggest an efferent arteriolar vasodilatation. Nevertheless, it should be emphasized that the individual reaction was variable, with sometimes a considerable fall in renal function. The reaction could neither be predicted from either the underlying cause of the chronic renal insufficiency, nor from the initial severity of renal function loss. The studies directed towards the possible preservation of renal function with fish oil have been reported in patients with IgA nephropathy. The results are contradictory. Therefore the verdict regarding the usefulness of fish oil on renal function in patients with chronic renal insufficiency remains open. In view of the above considerations the present study was undertaken to evaluate the role of PUFA in the prevention of progression of chronic renal disease, effect on proteinuria and lipid metabolism in patients with chronic renal disease (Reddy et al., 2002). In this review article, the impact of dietary fat and polyunsaturated fatty acids on chronic renal diseases is reviewed and structure some such compound is given in Fig. 1.

**Omega-3 fatty acids (\( \omega-3 \) FAs)**

These FAs are a family of USFAs that have in common a final carbon–carbon double bond in the \( n-3 \) position; that is, the third bond from the methyl end of the FA. Important nutritionally essential \( n-3 \) FAs include \( \alpha \)-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), all of which are polyunsaturated. The human body cannot synthesize \( n-3 \) FA *de novo*, but it can form 20-carbon unsaturated \( n-3 \) FAs (like EPA) and 22-carbon unsaturated \( n-3 \) FAs (like DHA) from the eighteen-carbon \( n-3 \) FAs ALA. These conversions occur competitively with \( n-6 \) FAs, which are
essential closely related chemical analogues that are derived from LA. Both the n-3 ALA and n-6 LA are essential nutrients which must be obtained from food. Synthesis of the longer n-3 FAs from LA within the body is competitively slowed by the n-6 analogues. Thus accumulation of long-chain n-3 FAs in tissues is more effective when they are obtained directly from food or when competing amounts of n-6 analogs do not greatly exceed the amounts of n-3.

History

Although omega-3 FAs have been known as essential to normal growth and health, awareness of their health benefits has dramatically increased in the past few years (Holman, 1998). The health benefits of the long-chain n-3 FAs-DHA and EPA n-3- are the best known. The high level of n-3 FAs consumed reduced heart rate, blood pressure, and atherosclerosis. The importance of DHA n-3, supports the normal development of the brain, eyes and nerves (Gardner, et al., 1996; ILSI North America, 1997). n-3 FAs which are important in human nutrition are: ALA, EPA, and DHA. These three polyunsaturates have either 3,5 or 6 double bonds in a carbon chain of 18, 20 or 22 carbon atoms, respectively. All double bonds are in the cis-configuration. Most naturally-produced FAs (even number of carbon in chains) are in cis-configuration where they are more easily transformable. The trans-configuration results in much more stable chains that are very difficult to further break or transform, forming longer chains that aggregate in tissues and lacking the necessary hydrophilic properties. However, n-3 compounds are still more fragile than n-6 because the last double bond is geometrically and electrically more exposed, notably in the natural cis configuration.

Health benefits

The 18 carbon ALA has not been shown to have the same cardiovascular benefits as DHA or EPA. Health promoting ‘omega 3’, but contain only ALA, not EPA or DHA. These products contain mainly higher plant oils and must be converted by the body to create DHA and therefore considered less efficient. DHA and EPA are made by microalgae that live in seawater. These are then consumed by fish and accumulate to high levels in their internal organs. If a person has ethical concerns about killing fish, or is concerned about mercury and oceanborne contaminants in fish, DHA can be produced directly from microalgae as a vegetarian source. People with certain circulatory problems, such as varicose veins, benefit from such supplements containing EPA and DHA which stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation, and additionally have been shown to reduce blood pressure (William, 2003). There is strong scientific evidence that n-3 FAs reduce blood triglyceride levels (Davison et al., 2007; Bucher et al., 2002) and regular intake reduces the risk of secondary and primary heart attack (Neil. 1996; Fortin et al., 1995). Some benefits have been reported in conditions such as rheumatoid arthritis (RA) (Jeppe et al., 1995) and cardiac arrhythmias (Pignier, et al., 2007; Kuan-Pin et al., 2003). There is preliminary evidence that n-3 FAs supplementation might be helpful in cases of depression (Naliwaiko, et al., 2004; Pinna et al., 2006) and anxiety (Pinna et al., 2006; Yehuda et al., 2005; Alexandra, 2006). Studies report highly significant improvement from n-3 FAs supplementation alone and in conjunction with medication and found no connection between depression in heart patients and supplements containing n-3 FAs (Keli, et al., 1994). Some research suggests that PUFA intake may reduce the risk of ischemic and thrombotic stroke (Iso, et al., 2001). However, very large amounts may actually increase the risk of hemorrhagic stroke. Lower amounts are not related to this risk, 3 grams of total EPA/DHA daily are considered safe with no increased risk of bleeding involved (De Deckere, 1999) and many studies used substantially higher doses without major side effects (Naliwaiko, et al., 2004; Tribole, 2006; van de Rest et al., 2008).

Dietary sources: A growing body of literature suggests that higher intakes of ALA, EPA, and DHA may afford some degree of protection against CHD. Because the physiological potency of EPA and DHA is much greater than that for ALA, it is not possible to estimate one AMDR for all n-3 FAs. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA (Becker mann, et al., 1990). A perceived risk of fish oil n-3 supplementation has been heavy metal poisoning by the body's accumulation of traces of heavy metals, in particular mercury, lead, nickel, arsenic and cadmium as well as other contaminants (PCBs, furans, dioxins, PBDEs), which potentially might be found especially in less-refined fish oil supplements. However, in reality, heavy metal toxicity from consuming fish oil supplements is highly unlikely. This is because heavy metals selectively bind with protein in the fish flesh rather than accumulate in the oil. An independent test in 2006 of 44 fish oils on the US market found that all of the products passed safety standards for potential contaminants. The FDA recommends that total dietary intake of n-3 FAs from fish not exceed 3 gm/day, of which no more than 2 gm/day are from nutritional supplements. The most widely available source of EPA and DHA is cold water oily fish such as salmon, herring, mackerel, anchovies and sardines. Oils from these fish have a profile of around seven times as much n-3 as n-6. Other oily fish such as tuna also contain n-3 in somewhat lesser amounts (Andrew and Sperling, 2007). The studies that compare bioavailability of the triglyceride form of fish oil vs. the ester form, two have concluded that the natural triglyceride form is better, and the other two studies did not find a significant difference. No studies have shown the ester form to be superior although it is cheaper to manufacture (Jennifer. 2007; Trebunová, et al., 2007).
Although fish is a dietary source of n-3 FAs, fish do not synthesize them; they obtain them from the algae or plankton in their diet.

**Unsaturated fats- Mono and Polyunsaturated fat; Omega fatty acids: ω−3; ω−6; ω−9**

**The n−6 to n−3 ratio:** Both n−3 and n−6 FAs are essential, i.e. humans must consume them in the diet. n−3 and n−6 compete for the same metabolic enzymes, thus the n−6:n−3 ratio will significantly influence the ratio of the ensuing eicosanoids (hormones), (e.g. PGs, LTs, TXs etc.), and will alter the body's metabolic function. Generally, grass-fed animals accumulate more n−3 than do grain-fed animals which accumulate relatively more n−6. Metabolites of n−6 are significantly more inflammatory (esp. AA) than those of n−3. This necessitates that n−3 and n−6 be consumed in a balanced proportion; healthy ratios of n−6:n−3 range from 1:1 to 4:1. Studies suggest that the evolutionary human diet, rich in game animals, seafood and other sources of n−3, may have provided such a ratio. Typical Western diets provide ratios of between 10:1 and 30:1 - i.e., dramatically skewed toward n−6. Here are the ratios of n−6 to n−3 FAs in some common oils: canola 2:1, soybean 7:1, olive 3−13:1, sunflower (no n−3), flax 1:3, cottonseed (almost no n−3), peanut (no n−3), grapeseed oil (almost no n−3) and corn oil 46 to 1 ratio of n−6 to n−3 (Hibbelp et al., 2006; William. 2003; Ohara. 2007; Robson. 2006).

Spontaneous renal diseases are a frequent cause of illness and death. This process serves as a model of progressive renal injury in this species (Finco et al. 1992) and of the effects of nutrients on progression of renal failure (Brown et al. 1991a, Finco et al. 1992b). The composition of dietary PUFAs modifies the course of induced renal disease in rats (Logan et al. 1992). In some laboratory studies (Clark et al. 1991), dietary supplementation with (n-3) PUFA is renoprotective; however, in others (Logan et al. 1992), PUFA supplementation was associated with worsening glomerulosclerosis and/or decrements in GFR. Results of studies in human beings are similarly conflicting, with benefits (Donadio et al. 1994) or no effect (Clark et al. 1993) reported. Because the response of dogs with renal insufficiency to dietary modification often differs from that observed in other species, several issues related to the effects of dietary PUFA supplementation in dogs remain unanswered (Brown et al., 1998).

**Role of PUFA and chronic renal diseases:** When dogs with a diverse array of spontaneous renal diseases were studied, they exhibited alterations in vasoactive urinary eicosanoid excretion, changes interpreted to support a role for glomerular hyperfiltration in progressive canine renal injury (Crocker et al. 1996). Because a variety of renal diseases were studied in this report, there is apparently a generalized effect of reduction in renal function on urinary eicosanoid metabolism. Eicosanoids produced from (n-3) PUFA are less vasoactive than those derived from (n-6) PUFA. Thus, dietary PUFA supplementation would be expected to alter renal production of eicosanoids and perhaps change the intrarenal hemodynamic response to disease. Although studies in dogs with spontaneous renal diseases indicated that GFR might increase in response to (n-6) PUFA supplementation (Bauer et al. 1997), the mechanism of this increase in GFR was not determined. Such an increase in GFR is likely due to an increase in glomerular capillary pressure or glomerular ultrafiltration coefficient. Earlier micropuncture studies (Brown et al. 1990 and 1991b) demonstrated that glomerular capillary pressure is increased in dogs with induced renal insufficiency and that the magnitude of this intrarenal hypertension is proportional to the degree of renal insufficiency. This change is referred to as glomerular capillary hypertension. Although no conclusive data are available in dogs with spontaneous renal diseases, a similar degree of glomerular capillary hypertension was observed in a dog with a spontaneous hereditary nephropathy. Glomerular capillary hypertension results from vascular changes that occur in adaptation to loss of renal function. These elevated intrarenal pressures are believed to contribute to renal injury, thereby causing progression of renal failure. In support of this contention, therapy that reduces the extent of glomerular hypertension (Brown et al. 1993) was beneficial to uni-nephrectomized dogs with alloxan-induced diabetes (Gaber et al. 1994). Intrarenal hemodynamics are influenced by vasoactive renal eicosanoids, such as prostaglandin E2 and thromboxane A2 (Schmitz et al. 1991). Dietary PUFA may serve as the precursor for these vasoactive compounds, and eicosanoids derived from (n-6) PUFA are more vasoactive than those derived from n-3 PUFA. Thus, changes in dietary PUFA composition modify glomerular hemodynamics in normal Sprague-Dawley rats (Schmitz et al. 1991). However, given the dramatic changes in glomerular function that occur after renal mass reduction, these results may not be applicable to dogs with renal insufficiency. Nonetheless, we hypothesized that dietary PUFA composition might alter intrarenal hemodynamics in dogs with renal insufficiency. To address this proposal, we studied the glomerular hemodynamic response to changes in dietary PUFA in dogs with induced renal insufficiency. Preliminary results of our studies demonstrated that dietary supplementation with n-6 PUFA raised, and n-3 PUFA lowered glomerular capillary pressure (Brown et al. 1996). Although there was no apparent increase in GFR in the group supplemented with n-6 PUFA, an increase of glomerular capillary pressure would be expected to increase GFR in some settings.

The glomerular hemodynamic studies revealed that n-6 PUFA increased, and n-3 PUFA reduced the magnitude of glomerular capillary hypertension. Thus we reasoned that the long-term effects of these dietary manipulations might be distinct. To address this hypothesis, we studied partially nephrectomized dogs randomly divided into three groups and
fed a diet supplemented with 15% fat from one of three alternate sources, i.e., safflower oil, beef tallow or menhaden fish oil (Brown et al. 1998). Although long-term supplementation with n-6 PUFAs (safflower oil) hastened progression of renal failure, supplementation with n-3 PUFAs (fish oil) was renoprotective. Progressive deterioration of renal function occurred in dogs receiving the safflower oil, n-6 PUFA, supplementation. These dogs also exhibited proteinuria; terminally, there was morphologic evidence of glomerular and tubulointerstitial injury. Dietary supplementation with beef tallow, a source of SFAs, was also associated with progressive decrements of renal function, although the rate of decline of renal function was slower in this group of dogs. In contrast, dietary supplementation with menhaden fish oil, a source of n-3 PUFA, prevented deterioration of GFR. This renoprotective maneuver also lessened the magnitude of proteinuria and preserved renal structure. Our findings of stable or increasing GFR in dogs fed the (n-3)—supplemented diet contrasts with our previous reports in dogs fed a low protein, low phosphorus diet for 24 mo after 94% nephrectomy (Brown et al. 1991a). In that study, decrements of GFR leading to end-stage renal failure (25% prevalence) were evident. In contrast, dogs fed the (n-3) PUFA-enriched diet had a mean overall increase in renal function and no dogs of this group developed end-stage renal failure. These results indicate that (n-3) PUFA were renoprotective, and n-6 PUFA deleterious in dogs after partial nephrectomy; this is consistent with those studies of n-3 PUFA demonstrating preservation of renal function and/or structure in rats after reduction of renal mass (Clark et al. 1991). In conclusion, dogs with spontaneous renal diseases exhibit alterations in vasoactive urinary eicosanoid excretion, changes consistent with a role for glomerular hyperfiltration in progressive canine renal injury (Crocker et al. 1996). Interestingly, short-term studies in dogs with naturally occurring renal disease indicate that supplementation with n-6 PUFA led to increased GFR (Bauer et al. 1997). On the basis of studies in dogs with induced renal disease (Brown et al. 1996), the mechanism of this increase in GFR appears to be an increase in glomerular capillary pressure. However, studies of the long term course of renal injury in dogs indicate that dietary supplementation with n-6 PUFA may hasten renal injury, perhaps through hypertensive glomerular injury (Brown et al. 1998). In contrast, dietary supplementation with n-3 PUFA lowered glomerular capillary pressure and was renoprotective. On the basis of studies to date, there is reason for optimism about the potential use of n-3 PUFA in the management of dogs with naturally occurring renal diseases. These potential benefits should be explored further in prospective clinical trials. 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.

Diet 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 CRF (Finco et al., 1992; Grandjean et al., 1990; Hansen et al., 1992; Leibetseder and Neufeld. 1991) although controversy exists regarding the level of protein restriction and at what stage such restriction may be needed (Kronfeld. 1993). The data regarding phosphorus restriction appear more convincing (Finco et al., 1992). Specific management recommendations based on stages of disease have recently been made (Brown. 1995). 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 diseases and have also been reported in dogs with both spontaneous and induced renal disease (Down and Krawiec 1995). 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)-resulting in increased concentrations of potentially atherogenic lipoproteins (partially metabolized lowdensity 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 (Attman et al., 1993). Increased serum cholesterol
concentration and a shift in 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 PUFAs (dihomo-γ-linolenic acid, AA, or 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 COX, whereas leukotrienes result from the action of various lipoxygenases. These compounds have extremely widespread and diverse effects, some of which may be of great importance in renal disease. The prostaglandins PGE2 and PG12 help to maintain renal blood flow and glomerular filtration in clinical conditions associated with renal compromise and are generally considered to be beneficial. PGI3 has been reported as having similar efficacy to PG12. Conversely, thromboxane A2 (TXA2) decreases renal blood flow and glomerular filtration. 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. Thromboxane A3 (TXA3) derived from EPA is biologically inert. 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 (Salvati et al., 1990; Takahashi et al., 1990; Schreiner and Klahr 1991). 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 (Crocker et al., 1996). Pharmacological or dietary intervention to alter these changes in eicosanoids may provide a means for modifying the disease process. Suppression of TX 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 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 (Down and Krawiec 1995). 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. 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. 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. 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 designed for the support of dogs with CRF has been investigated recently (McAlister et al., 1996; Malcik et al., 1996; Malcik. 1996). 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 (Fielding and Fielding. 1991).

Significant 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 rats with naturally developing focal glomerular sclerosis (Salvati et al., 1990); similar effects were seen in rats with subtotal renal ablation. 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 (Gonin-Jmaa and Senior 1995). This would be expected to decrease PGE2, PG12, and TXA2; however, PGE3 and PG13 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.
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. 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. 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.

Clearly, further research is necessary to evaluate better the potential for use of PUFAs 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 (Crocker et al., 1996; Bauer et al., 1997). The aims of this study were to compare urinary eicosanoid concentrations in normal dogs and those with naturally occurring CRF and to evaluate the impact of safflower oil (SFO) or menhaden fish oil (MFO) supplementation in dogs fed phosphorus- and protein-restricted diets. 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 FA analysis. TXB2 and PGE2 concentrations were measured in free catch urine samples by ELISA, with PGE2 first extracted on C18 silica columns. 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 (Attman and Alaupovic, 1991; Levey et al., 2006; Scher and Pillinger, 2005; Schmitz et al., 1991; Simopoulos, 2003).

The most common renal disease in both the groups was diabetic nephropathy and the disease frequency was similar in both the groups. Both the groups were matched in baseline parameters like blood pressure, biochemical parameters - blood urea, serum creatinine, proteinuria, serum albumin, serum cholesterol and serum triglycerides. There was no statistically significant difference in blood pressure, hemoglobin and blood urea levels at the end of follow up in both the groups when compared to baseline levels. There was decrease in proteinuria by 42% in group I where as proteinuria has increased by 33% in group II but it was statistically not significant. Serum albumin levels increased in both the groups but more so in group I but it was not statistically significant. In both the groups there was decrease in triglyceride and cholesterol levels but it was more in group II and the reduction in cholesterol in group II was statistically significant. The relationship of total plasma PUFAs, n-3 FA, LA, n-6 FA, linoleic acid, AA, and creatinine at enrollment with change in creatinine from baseline to follow-up was examined using multivariate linear regression models adjusted for covariates, including age, sex, BMI, education, cigarette smoking, energy intake, alcohol intake, LDL cholesterol, HDL cholesterol, cancer, cardiovascular disease, and hypertension. At enrollment, total plasma PUFAs and n-6 FA were significantly associated with lower creatinine. Adjusting for baseline creatinine, higher total plasma PUFAs, n-3 FA, linolenic acid, LA, and AA at enrollment were significantly associated with a smaller decline in creatinine from baseline to follow-up. Excluding participants with creatinine clearance 60 mL/min at baseline, and adjusting for multiple confounders, those with higher plasma PUFAs at enrollment had a lower risk of developing renal insufficiency, defined by a creatinine clearance 60 mL/min at the 3-year follow-up. Participants with higher plasma N-6 and N-3 FAs tended to have a lower risk of developing renal insufficiency, although this trend was not statistically significant. N-3 FA concentrations were inversely associated with risk of developing renal insufficiency.

DISCUSSION

This study shows that older adults with low total plasma PUFA concentrations have a greater decline in creatinine and creatinine clearance over 3 years of follow-up than those with higher concentrations of total plasma PUFAs. In addition, participants with lower baseline plasma PUFAs and free of renal insufficiency were significantly more likely to develop renal insufficiency at the 3-year follow-up than those with higher plasma PUFAs. These findings suggest that a higher dietary intake of PUFAs, both n-3 FA and n-6 FA, may be protective against progression to chronic kidney disease, and are consistent with observations from animal models that show that PUFA supplementation reduces progression of renal disease (Baggio et al., 2005). The observation that total plasma PUFAs and also ω-3 FAs and omega-6 FAs separately appear to have a beneficial effect on renal function require consideration. In fact, ω-3 PUFAs are generally considered more beneficial than ω-6 FAs (Simopoulos et al., 2000). However, recent data showed that both ω-6 (Kapoor and Huang, 2006) and ω-3 (Kim et al., 2004) FAs have anti-inflammatory properties. PUFAs are present in high concentrations not only in fish oil but also in vegetable oils. For example, large quantities of ω-6 FAs are present in sunflower oil, soybean/corn oil, and safflower oil, whereas large quantities of ω-3 FAs are present in flax oil and hemp oil. To our knowledge, this is the first human study that clearly observed a protective effect of PUFA on the age-associated decline of renal function. Strengths of this study are the relatively large sample size and the prospective, longitudinal analysis. The
study is limited in that plasma PUFA levels were measured only at enrollment and not at the 3-year follow-up visit. Also, the loss of some respondents to follow-up may have influenced our findings. The mechanisms by which PUFAs may protect the kidneys from damage in older adults remain unknown. The PUFAs may be antiinflammatory (Baggio et al., 2005). The main histopathological changes associated with the progression of renal disease in older adults are fibrosis, glomerulonephritis, progressive tubulointerstitial injury, and renal fibrosis (Baggio et al., 2005). In addition, experimental data have clearly shown that aging is associated with increased oxidative stress (Kim et al., 2004), enhanced tubular cell apoptosis (Qiao et al., 2005), and exacerbation of glomerular inflammatory responses induced by glomerular fibrin deposition (Xi et al., 2005). Dietary fish oil supplementation has been shown to reduce progression of renal disease among patients with IgA nephropathy (Donadio et al., 1994) and to suppress mesangial cell activation and proliferation in animal models (Grande et al., 2000). PUFAs may reduce inflammation through several possible pathways, such as reduction of nitric oxide (Das, 2004), downregulation of TNF-α (Kielar et al., 2003), and modulation of protein kinases (de Jonge et al., 1996). Plasma PUFA concentrations have previously been associated with lower levels of markers of inflammation in the InCHIANTI study (Ferrucci et al., 2006); in the present analysis, markers of inflammation were not included as confounders in the analysis because proinflammatory cytokines are considered to be in the causal pathway between plasma PUFAs and progression of renal disease (Baggio et al., 2005; Locatelli et al., 2003). A recent double-blind, placebo-controlled trial in 103 middle-aged men and women showed that increased dietary intake of ALA lowered CRP levels (Bemelmans et al., 2004). Another trial involving 60 subjects with active RA showed that n-3 FA supplementation decreased CRP (Sundarajan et al., 2004). Our findings prompt the hypothesis that a diet rich in PUFAs may be protective against the decline in renal function that is common with aging. A Mediterranean style diet that is characterized by a relatively high consumption of fish and low consumption of saturated fats has been shown to be protective against CVD (de Lorgeril and Salen, 2006; Zatonski and Willett, 2005), markers of inflammation (Zampelas et al., 2005), and cancer (Serra-Majem et al., 2006). Further work is needed to confirm the association between plasma PUFAs and renal function in other cohorts of older persons and provide enough evidence to translate these findings into clinical trials (Lauretani et al., 2008). There are many animal studies in which fish oils were shown to be beneficial in retarding the progression of renal failure (Brown et al., 1998; Melhado et al., 1992). In the present study the rate of rise in creatinine is lower in the PUFA group but it was not statistically significant. In a study, 8 weeks supplementation with omega-3 FAs in chronic renal disease resulted in preservation of GFR and effective renal plasma flow (Melhado et al., 1992). In study (Cappelliet al., 1997), 12 months treatment with 3.4 gms of PUFA daily resulted in decrease in triglyceride levels, reduced the rate of reduction of creatinine clearance and proteinuria. Long term studies directed towards the possible effects of fish oils in preservation of renal function in IgA nephropathy are contradictory. The beneficial effect and larger prospective studies did not confirm the initial positive findings. There was reduction in proteinuria and increase in serum albumin in PUFA group though it was statistically insignificant. In another study (Raffaele De Catenna, et al., 1993), administration of 7.7 gm of PUFA /day in patients with chronic glomerular disease resulted in significant reduction in proteinuria. The ineffectiveness of PUFA in preserving renal function and decreasing proteinuria may be due to the lower dose of PUFA used in our study when compared to the other studies. PUFA consistently decreased triglycerides in various studies and the effect is thought to result from inhibition of hepatic triglyceride synthesis. In the present study there was statistically significant decrease in cholesterol levels in the control group whereas in the PUFA group there was no significant decrease in triglyceride and cholesterol levels. In one study the lipid lowering effects of PUFA were more when the initial level of triglycerides was high. In our study the insignificant lipid lowering effect may be due to lower base line levels of lipids.

CONCLUSION

High PUFA concentrations, both n-3 FA and n-6 FA, may attenuate the age-associated decline in renal function among older community-dwelling women and men. 2008 American Association for Clinical Chemistry Chronic kidney disease is emerging as a major public health problem among older adults and can result in end-stage renal disease with need for dialysis or transplantation for kidney failure (Stevens et al., 2006; Xue et al., 2001). In the US, an estimated 19 million adults are in the early stage of disease (Stevens et al., 2006). The research showed that up to 12% of the adult population had some renal impairment (de Zeeuw et al., 2005). Creatinine clearance is widely used to assess chronic kidney disease in clinical practice and large epidemiologic studies (Giannelli et al., 2007; Fried et al., 2001). The major risk factors for chronic kidney disease are increasing age, hypertension, diabetes, cardiovascular disease, and a family history of the disease (Stevens et al., 2006). Abnormalities in lipids and atherogenic lipoprotein metabolism may contribute to glomerular and interstitial injury and progression of renal disease (Giannelli et al., 2007). Recent studies suggest that there may be an association between PUFAs (Calder, 2002) and the development of chronic kidney disease (Baggio et al., 2005). PUFA supplementation has been shown to reduce renal inflammation and fibrosis in animal models (Baggio et al., 2005). PUFAs may protect kidney function by modulating the inflammatory response through down regulation of the production of proinflammatory cytokines, COX-2 activity, and expression of endothelial leukocyte adhesion molecules (Calder, 2002; de Caterina et al., 2005). Accordingly, among older adults, high levels of plasma PUFAs were associated with lower levels of C-reactive protein (CRP) and proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF) and
higher levels of antiinflammatory cytokines such as IL-10 and transforming growth factor (TGF) (Ferrucci et al., 2006). We hypothesized that low total plasma PUFA levels were associated with an accelerated decline of kidney function in older adults.

REFERENCES


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