MINIREVIEW

Polyunsaturated Fatty Acids and Renal Disease (44031)

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Abstract. **An upregulation of arachidonate metabolism often accompanies renal pathophysiologic states. The resulting eicosanoids contribute to, or modify, the underlying process. Recent investigations suggest that platelet-neutrophil interactions, as well as alterations in the expression of the inducible isoform of cyclooxygenase, play a critical role in mediating changes in arachidonate metabolism in renal inflammation. The importance of arachidonate to renal pathophysiology has been highlighted by prior investigations which have demonstrated a beneficial effect of dietary polyunsaturated fatty acid (PUFA) modulation in a variety of models of experimental renal disease. More recent work has established that this beneficial effect may depend upon alterations in both lipid mediator generation as well as changes in cell function. In light of the benefits of dietary PUFA modulation in models of experimental renal disease, there have been numerous recent clinical trials of dietary (n-3) PUFA supplementation in patients with a variety of renal disorders. These clinical trials suggest that such therapy may be an important addition to the clinical armamentarium, especially in the treatment of IgA nephropathy.** [P.S.E.B.M. 1996, Vol 213]

In 1991, a minireview entitled, "Diet and Kidney Disease: The Role of Dietary Fatty Acids" was published in this journal (1). At the time, it was apparent that arachidonate metabolism was upregulated in renal disease states and that eicosanoids were critical modulators of the disease process. In general, the data suggested that prostaglandin E_2 (PGE_2) subserved a beneficial role through preservation of renal hemodynamics and immunosuppression, a role that was opposed by the actions of thromboxane A_2 (TxA_2) and leukotrienes. Existing studies further suggested that arachidonate metabolism in experimental renal disease could be manipulated in an advantageous fashion by dietary fatty acid manipulation, particularly, essential fatty acid (EFA) deprivation and (n-3) fatty acid supplementation.

In the interim, our understanding of the role and regulation of arachidonic acid in renal pathophysiology has evolved substantially. Additionally, our understanding of the beneficial mechanisms underlying dietary fatty acid manipulation has advanced, and a number of clinical trials applying this strategy to human renal disease have been published. The intent of this review is to summarize recent work on the role of fatty acids in renal disease. Although of necessity the current review will partially overlap our prior one as well as other recent reviews of this subject (2), our intent is to focus specifically on:

- new insights into the regulation and role of arachidonic acid metabolism in renal pathobiology;
- our current understanding of the immunologic effects of dietary polyunsaturated fatty acid (PUFA) manipulation;

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0037-9727/96/2131-0013$10.50/0

- the present status of the use of dietary PUFA manipulation in clinical renal disease states.

In the first section, we will specifically consider recent investigations on the regulation of arachidonic acid metabolism in renal inflammation and the relevance of the recently described inducible isoform of cyclooxygenase, cyclooxygenase-2 (COX-2) to renal disease. In the second section, we will summarize our current understanding of how dietary fatty acid modulation alters lipid mediator generation and leukocyte function examining data from both EFA deficiency and (n-3) PUFA modulation studies. In the third section, we will review data concerning the clinical utility of dietary fatty acid modulation with respect to renal diseases, summarizing available work on lupus nephritis, renal transplantation, chronic renal failure, and IgA nephropathy.

New Insights into the Regulation and Role of Arachidonic Acid Metabolism in Renal Pathobiology

Cellular and Molecular Mechanisms Underlying the Alteration of Arachidonate Metabolism in Renal Inflammation. Renal inflammatory states are often accompanied by an upregulation in local eicosanoid production that may play an important role in the accompanying pathophysiology. Glomerulonephritis, hydronephrosis, and interstitial nephritis are all characterized by a marked increase in the generation of arachidonic acid metabolites (3–11). TxA_2 and leukotrienes serve to promote the inflammatory response and to impair renal blood flow and function through effects on the renal vasculature, platelets, leukocytes, and mesangial cells (12, 13). These actions are opposed by those of PGE_2, prostacyclin, and other lipoxygenase metabolites of arachidonate (12, 13). The pleiotropic effects of eicosanoids in the kidney are mediated by a family of eicosanoid receptors, a subject that has recently been reviewed (14).

Although it has been appreciated that leukocytes play a pivotal role in the alterations in renal arachidonate metabolism during inflammation (10, 15), the specific cellular and molecular mechanisms underlying the upregulation in renal arachidonate metabolism have only recently been elucidated. To understand these mechanisms requires an appreciation of the immunology of the renal inflammatory response. Using glomerulonephritis as a paradigm, the acute phase of the renal inflammatory response is characterized by the influx of platelets and neutrophils into the glomerulus (16). This acute phase is followed by a more chronic influx of monocytes/macrophages into the inflammatory site, and these cells may interact with the resident mesenchymal cells (e.g., the mesangial cell within the glomerulus) (16–18). This interaction appears to be critical to the evolution of the inflammatory lesion, affecting specifically whether local scarring (e.g., glomerulosclerosis) takes place.

In studies performed recently (summarized in Fig. 1), neutrophils and platelets were found to be cooperatively essential for the upregulated production of eicosanoids and the accompanying glomerular dysfunction that occurs in acute glomerulonephritis (19–22). As noted above, acute nephritis is accompanied by a marked increase in glomerular eicosanoid production, particularly TxA_2, PGE_2 and leukotriene production (3–5). The aforementioned studies suggest that these metabolic alterations are due to an increase in glomerular cyclooxygenase, thromboxane synthase, and 5-lipoxygenase activity with little change in PGH-PGE isomerase or leukotriene A (LTA) hydrolase activities (19). In preparations of dissociated glomerular cells, the increase in 5-lipoxygenase activity and cyclooxygenase activities can be directly related to the presence of neutrophils in the inflamed glomerulus (19). However, the increase in thromboxane synthase appears to depend on the presence of both neutrophils and platelets (19).

This dependence of increased thromboxane synthase on both neutrophils and platelets appears to be due to their cooperative relationship in terms of migration into the inflamed glomerulus (19). Neutrophils serve to import platelets (and consequently their thromboxane synthase activity) into the glomerulus during nephritis through an adherence interaction which remains to be defined (see below). Platelets,

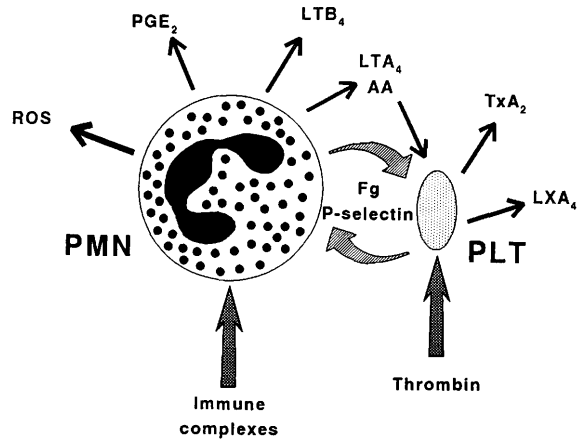

Figure 1. Role of neutrophil-platelet interactions in regulating arachidonic metabolism in acute glomerulonephritis. Neutrophils (PMNs) co-migrate into glomeruli with platelets (PLTs) and are cooperatively activated by inflammatory stimuli. Neutrophils release prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4), and also provide arachidonate and LTA_4 to platelets for transcellular metabolism to thromboxane A_2 (TxA_2) and lipoxin A_4 (LXA_4), respectively. Neutrophils also produce reactive oxygen species (ROS) which may contribute to glomerular damage. The co-migration and co-activation of these cells are mediated by fibrinogen (Fg) and P-selectin.

conversely, are required for the efficient migration of neutrophils into the inflamed glomerulus. Thus, the increase in glomerular leukotriene B_4 (LTB_4) synthesis is also dependent (albeit indirectly) on the presence of platelets due to their effects on neutrophil migration (19). In addition to their cooperative role in the regulation of arachidonate metabolism in acute nephritis, neutrophils and platelets both appear to be essential for the acute glomerular dysfunction (as manifested by proteinuria) that occurs concomitantly (19).

Upregulation of glomerular lipoxin synthesis is also observed in acute glomerulonephritis (20). Synthesis of lipoxins is similarly dependent on the presence of both neutrophils and platelets within inflamed glomeruli. *In vitro* data suggest that the mechanism underlying this metabolic alteration is the transcellular metabolism by platelets of LTA_4 released by neutrophils. Lipoxins may play a potential counterregulatory role in renal inflammation, specifically antagonizing the effects of leukotrienes on leukocyte adhesion (23).

Studies have also investigated the basis of the platelet-neutrophil interaction which is essential for the altered glomerular arachidonate metabolism in nephritis. In particular, recent work has established that fibrinogen plays an important role in platelet-neutrophil co-activation both *in vitro* and in the context of nephritis *in vivo*. A marked upregulation in glomerular expression of the platelet fibrinogen receptor, $\alpha_{IIb}\beta_3$, is apparent in acute nephritis due to the local deposition of platelets that are imported into the glomerulus by neutrophils (21). Fibrinogen, moreover, appears to contribute to the evolution of proteinuria during acute nephritis, which is felt to result from reactive oxygen species elaborated from neutrophils (21). *In vitro* data further suggest that fibrinogen may serve to mediate the ability of platelets to activate the respiratory burst by neutrophils (21).

Other studies suggest that P-selectin may mediate the platelet-neutrophil interaction. If P-selectin is blocked with a function-inhibiting monoclonal antibody, the increase in glomerular lipoxin synthesis that occurs in acute nephritis is markedly inhibited (20). Similarly, this monoclonal antibody blocks lipoxin production by platelet-neutrophil co-incubations *in vitro*. Additionally, glomerular lipoxin synthesis is attenuated during nephritis in P-selectin deficient mice, and can be restored by the infusion of normal platelets (22).

The mechanisms underlying platelet-neutrophil co-migration into glomeruli, in contrast, remain to be clarified. Fibrinogen appears to play a modest role in the co-migration of these cells (21). Although a logical choice as a mediator of platelet-neutrophil co-migration would seem to be P-selectin, the aforementioned monoclonal antibody to P-selectin does not diminish neutrophil migration into glomeruli as does platelet depletion (19–21). Moreover, the influx of neutrophils is increased during nephritis in P-selectin deficient mice (22).

Prior studies have suggested an important role for leukotrienes in acute glomerulonephritis. As noted above, leukotriene production is markedly upregulated in inflamed glomeruli (4, 5), and peptidoleukotrienes appear to participate in the acute decrease in renal function that occurs in this setting (24, 25). Whether or not LTB_4 is active as a neutrophil chemoattractant in this disease model is unsettled (26, 27). The recent availability of 5-lipoxygenase deficient mice has allowed for a reassessment of this issue using a model that is not dependent on pharmacologic manipulation. Mice deficient in 5-lipoxygenase exhibit a mild phenotype, with an inflammatory response that is more highly dependent on prostaglandins (28). Of note, recent work using 5-lipoxygenase–deficient mice has demonstrated that immune complex glomerulonephritis is as severe as in a control mice both in terms of functional changes and the inflammatory response (29).

These results suggest that a reevaluation of the role of 5-lipoxygenase metabolites in glomerulonephritis may be warranted. The lack of beneficial effect of 5-lipoxygenase deletion may reflect the complex interplay between pro-inflammatory leukotrienes and anti-inflammatory 5-lipoxygenase metabolites such as the lipoxins (29). Alternatively, LTB_4 may play a subsidiary role to other chemoattractants. Specifically, recent work suggests that chemokines, such as interleukin-8 (or its murine homologues) may be more essential for neutrophil migration in acute nephritis (30, 31).

Cyclooxygenase-2 and Renal Pathophysiology. With the recent discovery of the inducible isoform of cyclooxygenase, referred to as COX-2 (32, 33), it has become apparent that the upregulated eicosanoid production in renal inflammation may result from the induction of this enzyme. Upregulation of COX-2 has recently been reported in both experimental glomerulonephritis (34) and hydronephrosis (35). Although the underlying immunologic mechanisms are as yet uncertain, both invading leukocytes (particularly macrophages) and mesangial cells have the capacity to express COX-2 (36, 37). Leukocytes are stimulated to express COX-2 *via* adherence to a substrate (38), while mesangial cells are stimulated to express COX-2 *via* cytokines (e.g., interleukin-1β [IL-1β]) elaborated by invading leukocytes (36).

COX-2 may also participate in renal pathophysiologic states other than inflammation. Recent work suggests an important role for COX-2 in modulating the effect of vasoconstrictors or mechanical stimuli, such as stretch, on mesangial cells (39, 40). COX-2 expres-

sion is also dramatically upregulated in the renal cortex (particularly the macula densa) during salt restriction (41). These studies suggest an important role for this enzyme in sodium, volume, and blood pressure homeostasis.

It appears that COX-2 may also play an important constitutive role in renal development. COX-2 is constitutively expressed in the macula densa and adjacent epithelial cells of the cortical thick lamb of Henle (41). Moreover, COX-2–deficient mice recently generated show severe renal pathology (42). Both small immature glomeruli and tubules are seen, along with evidence of progressive interstitial inflammation, interstitial fibrosis, and glomerulosclerosis. These changes appear to represent a postnatal arrest in nephrogenesis with overload of the reduced number of functional nephrons. In contrast, no renal abnormalities are noted in COX-1–deficient mice, suggesting a specific role for the COX-2 isoform (43).

The discovery of the inducible form of cyclooxygenase, COX-2, has led to the development of isoform specific inhibitors (44). These inhibitors appear to be effective anti-inflammatory agents with reduced gastric toxicity (44). The constitutive and induced expression of COX-2 in the kidney, however, suggests that recently developed specific inhibitors of this enzyme, while gastroprotective, may still cause nephrotoxicity in states of impaired volume regulation or renal inflammation similar to the nephrotoxicity associated with current nonspecific cyclooxygenase inhibitors. This speculation remains to be addressed experimentally.

Recent studies have suggested that there is an intimate interrelationship between nitric oxide ($NO^{\bullet}$) production and arachidonic acid metabolism during renal inflammation. Using the relatively specific inhibitor of the inducible nitric oxide synthase (iNOS), aminoguanidine, it was observed that inhibition of iNOS coordinately inhibited $NO^{\bullet}$ and prostaglandin production by the rabbit hydronephrotic kidney (35). Coordinate regulation between $NO^{\bullet}$ and prostaglandins was also observed *in vitro* in macrophages and fibroblasts, the major participants in the inflammatory response underlying hydronephrosis (45). Inhibition of $NO^{\bullet}$ synthesis by aminoguanidine in activated macrophages suppressed PGE_2 production. Moreover, $NO^{\bullet}$ increased cyclooxygenase activity (in terms of arachidonic acid conversion to PGE_2) in cytokine-stimulated fibroblasts.

The mechanism underlying the relationship between $NO^{\bullet}$ and cyclooxygenase remains to be fully clarified, although recent data suggest that this relationship may involve regulation of COX-2 expression. In the aforementioned work, the data support a direct activating effect of $NO^{\bullet}$ on the cyclooxygenase enzyme, possibly *via* an effect on the heme domain (45). A more recent study, however, has suggested that the effect of $NO^{\bullet}$ may be mediated *via* a transcriptional mechanism on COX-2 since $NO^{\bullet}$ did not increase constitutive PGE_2 formation but markedly augmented cytokine-induced PGE_2 production *via* an increased induction of COX-2 mRNA (46). This effect, moreover, appeared to be mediated *via* cGMP, the second messenger which typically transduces NO-mediated signals.

The products of cyclooxygenase may also act together to modulate the elaboration of $NO^{\bullet}$. It was recently observed that inhibition of cyclooxygenase with indomethacin enhances the induction of iNOS in response to IL-1β treatment and the consequent elaboration of $NO^{\bullet}$ by mesangial cells (47). This effect is reversed by exogenous PGE_2 but not prostacyclin (PGI_2). In contrast to PGE_2, PGI_2 enhances iNOS level and $NO^{\bullet}$ production most likely *via* the activation of adenylate cyclase. A hypothetical scheme for the complex interplay between COX-2 and NOS that occurs in renal inflammation is presented in Figure 2.

The role of $NO^{\bullet}$ in renal pathophysiology has also been the subject of intensive recent investigation. With respect to glomerulonephritis, it is clear that glomerular $NO^{\bullet}$ production is elevated with the onset of glomerular inflammation (48). Moreover, studies in several models of nephritis suggest that inhibition of $NO^{\bullet}$ synthesis protects against inflammatory damage and scarring (49, 50).

Immunologic Effects of Dietary Fatty Acid Manipulation

The salutary immunomodulatory effects of dietary PUFA manipulation on renal inflammation were noted

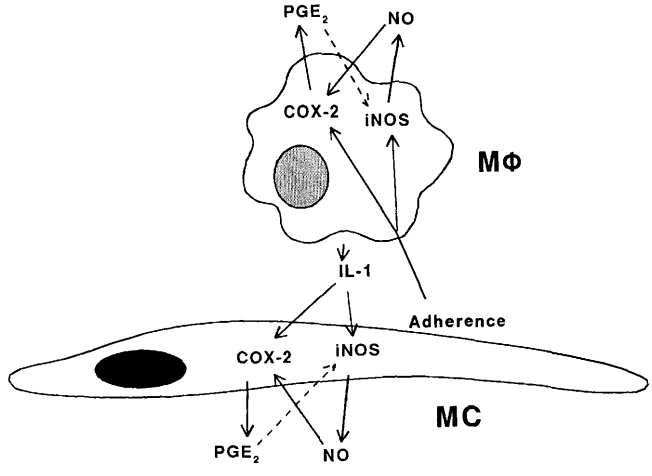

Figure 2. Interactions between COX-2 and iNOS in renal inflammation. Mesangial cells (MCs) are induced to produce the cyclooxygenase-2 isoform (COX-2) and the inducible nitric oxide synthase (iNOS) by interleukin-1 (IL-1) released from inflammatory cells (e.g., macrophages, Mϕs). Reciprocally, macrohpages are stimulated by adherence to produce COX-2 and iNOS as well. $NO^{\bullet}$ derived from iNOS drives COX-2 production, whereas PGE_2 produced from COX-2 inhibits iNOS production. Solid arrows, a positive effect, dashed arrows, a negative effect.

approximately 15 years ago with the finding that essential fatty acid (EFA) deficiency ameliorates the nephritis accompanying murine lupus (51). In the interval since then studies have shown that dietary PUFA manipulation (both EFA deprivation as well as [n-3] fatty acid supplementation) exerts an anti-inflammatory effect in many models of renal inflammation, including murine lupus glomerulonephritis (51–54), anti-GBM nephritis (55, 56), hydronephrosis (57), interstitial nephritis (58), Heymann nephritis (59), and glomerulosclerosis (60). In addition, substantial insight has been gained into the biochemical and immunologic mechanisms underlying the beneficial effect. In this section, we will consider the effects of dietary PUFA modulation on both the elaboration of lipid mediators and on leukocyte function. The available data are presented in summary form in Table I.

To clarify the discussion, the different families of PUFAs along with the appropriate nomenclature are displayed in Figure 3. There are three noninterconvertible families of PUFAs defined by the location of the terminal double bond: (n-9), (n-6), and (n-3) PUFAs. The (n-9) family can be endogenously synthesized by vertebrates, while the (n-6) and (n-3) families are derived strictly from dietary sources. The 20 carbon members of these three families serve as eicosanoid precursors. The predominance of an individual family of PUFAs within vertebrate cellular phospholipids is largely controlled by the diet. Normally, (n-6) PUFAs predominate; however, with PUFA deprivation, particularly (n-6) PUFAs (i.e. essential fatty acid [EFA] deficiency), the (n-9) PUFAs become the major PUFAs within phospholipids. Conversely, when the diet is supplemented with (n-3) PUFAs (usually derived from marine sources), (n-3) PUFAs become predominant.

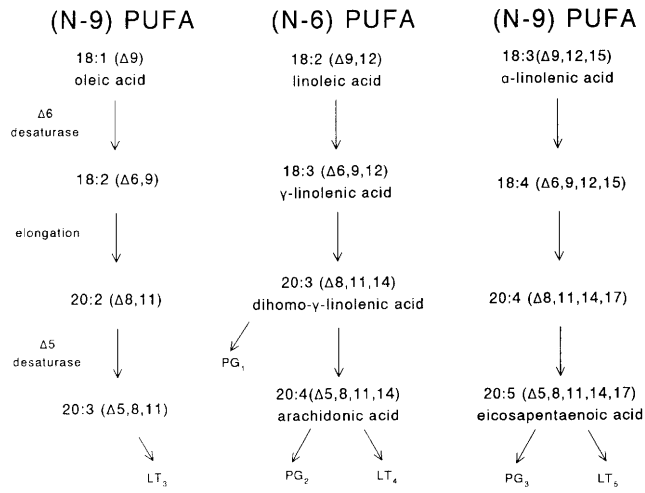

Figure 3. Polyunsaturated fatty acid nomenclature, biosynthesis, and metabolism. Polyunsaturated fatty acids (PUFAs) can be grouped into three families, designated (n-9), (n-6), or (n-3) depending on whether the last double bond is 9, 6, or 3 carbons in from the terminal carbon. The initial 18 carbon fatty acid in each family is converted by the same series of enzymes into 20 carbon PUFAs that serve as eicosanoid precursors. Metabolism to either a prostaglandin (PG) or leukotriene (LT) is indicated in the figure along with the number of double bonds in the resulting eicosanoid as a subscript. The various PUFAs are identified by the number of carbons and double bonds separated by a colon, with the location of the individual double bonds indicated in parentheses after Δ. Common chemical names are also provided. The widely used, more concise nomenclature specifying the number of carbons followed by the number of double bonds and the PUFA family in parentheses (e.g., 20:4[n-6]) is employed in the text.

Dietary PUFA Modulation and Lipid Mediator Generation. Dietary PUFA manipulation in part appears to exert its anti-inflammatory effects through alterations in prostaglandin production. The principal constituent of (n-3) PUFAs, eicosapentaenoic acid (20:5[n-3]) is a poor substrate for, but a potent inhibitor of, cyclooxygenase (61). Thus, 20:5(n-3) serves predominantly to inhibit the metabolism of arachidonic acid to prostaglandins of the 2 series. EFA deficiency, however, presents a distinctly different scenario. The fatty acid that accumulates in this state, 20:3(n-9), is not a particularly good substrate for cyclooxygenase, nor is it a potent inhibitor of the metabolism of arachidonic acid to prostaglandins (62, 63). Although the depletion of arachidonic acid and its replacement with 20:3(n-9) in EFA deficiency can reduce prostaglandin production in response to hormonal agonists, such as reduction is not an invariable property of this dietary manipulation (63, 64). Moreover, cyclooxygenase inhibition does not necessarily reproduce the anti-inflammatory effects of dietary

Table I. Immunologic Effects of Dietary Fatty Acid Modulation

	EFA deficiency	(n-3) PUFA supplementation
Lipid mediator production		
PG_2/Tx_2 generation	↓ →	↓ ↓ (↑ PG_3/Tx_3)
LTB_4 generation	↓ ↓	↓ (↑ LTB_5)
PAF formation	↓	↓ →
Leukocyte function		
Chemotaxis	↓	↓
Adherence	↓	?
Cytokine production	↓	↓
Respiratory burst	↓	↓
$NO^{\cdot}$ production	↓	↓

PUFA manipulation with respect to renal disease (51, 65). Thus, a decrease in prostaglandin synthesis cannot be the sole mechanism underlying the beneficial effect of dietary PUFA manipulation in renal disease.

In recent years, it has become clear that 20:3(n-9) or 20:5(n-3), which accumulate in lieu of arachidonate in EFA deficiency and dietary (n-3) PUFA supplementation, lead to marked alterations in LTB_4 formation. *In vitro* studies have established that 20:3(n-9) is metabolized to LTA_3 by the 5-lipoxygenase pathway and that LTA_3 is a very reactive epoxide which inhibits LTA hydrolase and prevents both its own metabolism to LTB_3 as well as the metabolism of LTA_4 to LTB_4 (66). A similar mechanism appears operative with respect to 20:5(n-3), which can be metabolized to LTA_5, although LTA_5 is a better substrate and a weaker inhibitor of LTA hydrolase (67). The relevance of these *in vitro* studies to the production of LTB by inflammatory cells and the inflammatory response *in vivo* has also been established (63, 68–70). Both EFA deficiency and dietary (n-3) supplementation alter the generation of LTB species *in vivo,* with EFA deficiency being the more potent manipulation.

In addition to these alterations in eicosanoid production, recent studies have reported that dietary PUFA modulation may suppress the production of platelet activating factor (PAF), although such suppression has not uniformly been observed with (n-3) PUFA supplementation (71–73). The decrease in PAF production with dietary PUFA modulation probably results from the replacement of arachidonate in alkyl-phosphatidylcholine with 20:3(n-9) (with EFA deficiency), or 20:5(n-3) and 22:6(n-3) (with [n-3] PUFA supplementation). This last PUFA is an especially poor substrate for the Ca-dependent cytoplasmic phospholipase A_2 ($cPLA_2$), which is the phospholipase probably responsible for lyso-PAF formation (74). In addition, 22:6(n-3) within alkyl-phosphatidylcholine may act as an inhibitor of the $cPLA_2$ (75). Speculatively, the variable effect of (n-3) PUFA supplementation on PAF formation may be attributable to variations in the 22:6(n-3) content of the supplement and the resulting incorporation of this fatty acid into inflammatory cells.

Dietary PUFA Manipulation and Leukocyte Function. It has also been observed that leukocytes exhibit certain functional alterations consequent upon dietary PUFA manipulation which cannot be attributed directly to changes in lipid mediator production. For example, neutrophil chemotaxis and superoxide production have both been shown to be decreased in neutrophils from animals and humans subjected to either EFA deficiency or (n-3) PUFA supplementation (76–78). It has also been observed that EFA deficiency may induce specific alterations in macrophage function (63, 79).

Of particular relevance to macrophage migration is the recent observation that EFA deficiency impairs the capacity of resident murine macrophages to adhere and spread (79). This alteration in macrophage function appears to be due to a reduction in the release of arachidonic acid (*via* phospholipase action) which occurs during adherence and spreading (79, 80). A similar relationship between adherence/spreading and arachidonate release has been observed in other cell types (81). The requirement for arachidonate does not appear to be mediated by a cyclooxygenase or 5-lipoxygenase metabolite, but may represent an autocrine effect of arachidonate *per se* (79).

Apropos of these observations, it has been observed that dietary (n-3) PUFA supplementation may inhibit cytokine production by mononuclear cells, particularly IL-1β and tumor necrosis factor–α (TNFα) (82). Reduction of cytokine production could potentially downregulate many subsequent pro-inflammatory events such as the expression of adhesion molecules on endothelium and the elaboration of chemokines. Although the mechanism underlying the reduced elaboration of cytokines with dietary (n-3) PUFA supplementation is uncertain, it is noteworthy that adherence is a principal stimulus for the expression of cytokines by these cells (83).

Dietary (n-3) PUFA supplementation and EFA deficiency have also been recently noted to lead to a reduction of $NO^{\cdot}$ production by macrophages, with a parallel reduction in TNF-α expression (84). The reduction in $NO^{\cdot}$ production is specific for that generated by iNOS. The mechanism underlying this decrease in $NO^{\cdot}$ elaboration, however, is uncertain. Dietary PUFA manipulation does not reduce iNOS induction or alter arginase activity. A reduction in $NO^{\cdot}$ production, however, would likely be of benefit in hindering the evolution of nephritis, based on the studies cited above.

Although we have focused primarily on the immunologic consequences of dietary PUFA manipulation, it is likely that the beneficial effects of (n-3) PUFA supplementation are also mediated *via* salutary effects on plasma lipids, blood pressure, and renal hemodynamics. The literature on such effects has been recently summarized (2). In addition, data suggest that PUFA manipulation may alter the response of mesangial cells, both in terms of proliferation and contractility (85, 86). Such effects may be of particular relevance to the beneficial effect of dietary (n-3) PUFA supplementation recently observed in IgA nephropathy (see below).

Current Status of the Use of Dietary Fatty Acid Manipulation in Clinical Renal Disease

As noted above, there is ample evidence that modulation of dietary fatty acids is of benefit in experimen-

tal models of renal disease. The data on (n-3) PUFA supplementation and renal disease have recently been reviewed (2). In light of these positive experimental studies, there has been substantial interest in applying dietary (n-3) PUFA modulation to clinical renal disease. In a number of studies performed over the past several years, the effect of dietary (n-3) PUFA modulation has been assessed in lupus nephritis, renal transplantation, chronic renal disease, and IgA nephropathy. The data on the utility of this therapy on each of these conditions are summarized below and presented in Table II.

Systemic Lupus Erythematosus. Dietary (n-3) PUFA supplementation in lupus nephritis patients was first examined several years ago in a preliminary study (87). This pilot study showed a beneficial response to the therapy in terms of decreases in both pro-inflammatory mechanisms and circulating lipid levels, although parameters of renal disease and autoimmunity were unaltered. Subsequently, two more comprehen-

Table II. Summary of Trials of (n-3) PUFA Supplementation in Clinical Renal Disease

Date of study	Patients (1)	Design	Dose (g/day)	Duration (months)	Benefit	Comments
SLE nephritis						
1989 (87)	12	o	6 or 18	1.25	+/−	Positive effect on lipids and inflammatory parameters. No effect on renal function.
1990 (89)	17	db,x	0.2 g/kg	6	−	Study of active lupus, not all patients had nephritis.
1993 (88)	12	db,x	15	12	−	Substantial carry-over and other effects. High probability of type II error.
Renal allografts—initial therapy						
1992 (90)	88	r,p	6	1	+	No difference in incidence of rejection, but better recovery of function post rejection.
1992 (92)	29	r	9	12	+	Better renal function, but no alteration in incidence of rejection.
1993 (91)	66	db	6	12	+	Better renal function, decreased rejection, improved graft survival.
Renal allografts—chronic therapy						
1989 (93)	14	o	0.2 g/kg	6	+	Decreased rate of deterioration.
1990 (94)	21	db	6	3	+	Better renal function, lower blood pressure.
1995 (95)	90	db	9 or 18	6.5	−	Poor overall compliance.
1995 (96)	18	o	6	2.5	−	
Chronic renal failure						
1987 (97)	15	o	3	2	+	Better renal function.
1991 (98)	7	o	3	3	+/−	Slightly better renal function, mixed effects on plasma lipids.
1992 (99)	8	o	15	1.5	+/−	Mixed effects on plasma lipids. Renal function not followed.
1993 (100)	14	o	9	1.5	+	Decreased proteinuria, lower blood pressure, improved plasma lipids.
IgA nephropathy						
1989 (101)	37	r	10	24	−	
1990 (102)	11	o	10	9	−	Patients had severe renal dysfunction.
1994 (103)	106	db	12	24	+	Marked effect on disease progression and mortality.

Note. o, open; db, double-blind; r, randomized; p, placebo-controlled; x, cross-over.

sive and better controlled trials were published (88, 89). Neither demonstrated a beneficial response of lupus nephritis to dietary (n-3) PUFA supplementation. Nonetheless, both of these more recent studies have limitations which mitigate an entirely negative conclusion. In one of the studies, lupus patients in general were examined, and not all of these had active nephritis (89). In addition, the number of patients studied was small. Thus, it is difficult to conclusively rule out a benefit. In the other study, the investigators noted both carry-over effects of fatty acid supplementation and a positive response to the placebo (olive oil) which may have altered their ability to observe a significant difference (88). Moreover, the authors' analysis of the power of this study suggested the strong possibility of type II error (88). Thus, the effect of dietary (n-3) PUFA supplementation on lupus nephritis remains uncertain.

Renal Transplantation. Dietary (n-3) PUFA supplementation has had appeal as a therapy for renal transplant patients, both as an anti-rejection therapy as well as a way to ameliorate the renal dysfunction due to cyclosporin. This therapy has been examined by several groups over the preceding few years in two different contexts: as the initial therapy for patients receiving renal transplants, and as a component of long-term therapy to prevent allograft rejection in patients with established renal allografts.

The data on the addition of (n-3) PUFA supplements to the initial therapy after renal transplantation seem fairly promising. One initial study of limited duration demonstrated better recovery of renal function post rejection in patients receiving (n-3) PUFA supplements, although the overall incidence in rejection was not diminished (90). In a longer term and better controlled follow-up study, the same investigators found that (n-3) PUFA supplements decreased the incidence of rejection, preserved renal function, and improved overall graft function (91). Studies by another group also suggest that renal function of newly transplanted kidneys may be preserved by (n-3) PUFA supplements (92). Although no decrease in rejection was noted in this study, the sample size was relatively smaller.

Results of studies on the use of (n-3) PUFA supplementation in patients with established allografts are more mixed. Although early studies suggested a potential benefit in terms of decreased rate of deterioration of renal function (93, 94), more recent studies have not confirmed this (95, 96). However, these latter studies were undermined either by poor compliance with the therapy or small sample sizes. Thus, the benefit of (n-3) PUFA supplements to renal allograft recipients with established allografts appears less certain than the benefit to patients with new transplants.

Chronic Renal Failure. Dietary (n-3) PUFA supplementation has also been used to treat a variety of chronic renal diseases in an effort to prevent disease progression. As noted above, the benefits of such therapy are not limited to immunologic effects but may also involve salutary effects on plasma lipids and blood pressure. Although the available data are suggestive of a benefit, the studies performed to date are too limited to allow firm conclusions at this time.

In an initial study, (n-3) PUFA supplements were noted to preserve renal function in a group of patients with a variety of conditions resulting in chronic renal failure, including chronic glomerulonephritis, interstitial nephritis, glomerulosclerosis, chronic pyelonephritis and polycystic disease (97). Subsequent studies of patients with various chronic renal diseases failed to confirm this benefit and noted mixed effects on plasma lipid levels (98, 99). However, the numbers of patients in these studies were quite small.

In the most recent study, the effects of (n-3) PUFAs were examined in patients with either membranous glomerulonephritis or focal glomerulosclerosis (100). There appeared to be an overall beneficial effect in terms of decreased proteinuria, decreased blood pressure, and improved lipid levels. On the basis of this study, a larger trial has been initiated and will hopefully further clarify the use of (n-3) PUFA supplementation in chronic renal failure (2).

IgA Nephropathy. Because of the lack of an effective therapy for IgA nephropathy and the potential of the condition to progress in certain patients, (n-3) PUFAs have been tried by several groups of investigators as a treatment for this disorder. In one early study, (n-3) PUFAs failed to benefit such patients regardless of their initial renal function (101). In a second study, (n-3) PUFA supplementation was also found to be of no benefit; however, the patients involved already had advanced renal dysfunction at the beginning of the study (102). The largest and best controlled series available does suggest a substantial benefit from (n-3) PUFA supplementation (103). In this study, deterioration of renal function was dramatically retarded in patients given (n-3) PUFA supplements. Additionally only 10% of patients receiving (n-3) PUFA supplements died or progressed to end-stage renal disease versus 40% of patients receiving placebo. In light of these results and the lack of an alternative effective therapy, (n-3) PUFAs would appear to be the preferred current treatment for IgA nephropathy.

Summary

Recent studies of arachidonate metabolism in the context of renal inflammation have substantially improved our understanding of the mechanisms underlying this metabolic alteration. It has become clear that the upregulated arachidonate metabolism which generally accompanies renal inflammatory states results

both from complex interactions between leukocytes and platelets, as well as the expression of the inducible form of cyclooxygenase by leukocytes and endogenous glomerular cells. The resulting alteration in arachidonate metabolism has the potential to modify the inciting inflammatory response *via* the elaboration of eicosanoids which may modify other mediator systems such as $NO^{\cdot}$.

Dietary PUFA manipulation appears to exert anti-inflammatory effects *via* alterations in eicosanoid production but may also alter leukocyte function in an eicosanoid-independent fashion. Regardless, dietary PUFA modulation appears to be a useful immunomodulatory manipulation which has found current clinical application. Specifically, dietary (n-3) PUFA supplementation appears to have substantial benefit in IgA nephropathy and may benefit renal transplant patients when added to the initial therapeutic regimen. It is also possible that such therapy may benefit patients with lupus nephritis or with chronic renal failure due to a variety of causes, although additional trials need to be performed.

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