The Role of Fish Oil/Omega-3 Fatty Acids in the Treatment of IgA Nephropathy

By James V. Donadio and Joseph P. Grande

Beneficial effects of omega-3 polyunsaturated fatty acids (n-3 PUFA) have been reported in recent epidemiologic studies and randomized clinical trials in a variety of cardiovascular and autoimmune diseases. Fish and marine oils are the most abundant and convenient sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major n-3 fatty acids that serve as substrates for cyclooxygenase and lipoxygenase pathways leading to less potent inflammatory mediators than those produced through the n-6 PUFA substrate, arachidonic acid. N-3 PUFA can also suppress inflammatory and/or immunologic responses through eicosanoid-independent mechanisms. Although the pathophysiology of IgA nephropathy is incompletely understood, it is likely that n-3 PUFA prevents renal disease progression by interfering with a number of effector pathways triggered by mesangial immune-complex deposition. In addition, potential targets of n-3 PUFA relevant to renal disease progression could be similar to those involved in preventing the development and progression of cardiovascular disease by lowering blood pressure, reducing serum lipid levels, decreasing vascular resistance, or preventing thrombosis. In IgA nephropathy, efficacy of n-3 PUFA contained in fish oil supplements has been tested with varying results. The largest randomized clinical trial performed by our collaborative group provided strong evidence that treatment for 2 years with a daily dose of 1.8 g of EPA and 1.2 g of DHA slowed the progression of renal disease in high-risk patients. These benefits persisted after 6.4 years of follow up. With safety, composition, and dosing convenience in mind, we can recommend two products that are available as pharmaceutical-grade fish-oil concentrates, Omacor (Pronova Biocare, Oslo, Norway) and Coromega (European Reference Botanical Laboratories, Carlsbad, CA).

THE HEALTH BENEFITS OF omega-3 polyunsaturated fatty acids (n-3 PUFA) have gained wide attention both in the medical literature and lay press. Favorable effects of n-3 PUFA in a variety of cardiovascular and autoimmune diseases are supported by an impressive number of studies reported over the past decade (Table 1). The evidence for these beneficial effects is based largely on epidemiologic studies and randomized clinical trials in which both fish consumption and fish oil supplements were tested for efficacy. In IgA nephropathy, only fish oil supplementation was used in the reported clinical studies.[1-6]

In this review, we discuss the biochemistry and food sources of essential fatty acids, and possible mechanisms, clinical studies, dose recommendations, and safety that support the use of n-3 PUFA in the treatment of patients with IgA nephropathy.

BIOCHEMISTRY AND FOOD SOURCES OF ESSENTIAL FATTY ACIDS

The essential fatty acids (EFA) are polyunsaturated fatty acids (PUFA) that are ubiquitous in cellular membranes of animals, including humans. The PUFA are nutrients required for normal function[7,8] and are diminished in the lipids of membranes in nutritional EFA deficiency. The content of PUFA in lipids of vital organs, including the kidney,[9] responds to changes in dietary EFA of both the n-6 and n-3 families. These two families of EFA are not interconvertible.

Mammals lack the ability to synthesize fatty acids with double bonds distal to the ninth carbon atom. Therefore, long-chain PUFA are essential to their diets (Fig. 1). Linoleic acid (C18:2n-6) is the parent n-6 PUFA found in oils of plant seeds such as corn, soy, and safflower. Linoleic acid contains two double bonds; the first double bond from the methyl carbon atom end is at the sixth carbon atom, thus, the designation n-6 PUFA (Fig. 1). Once consumed, linoleic acid elongates and desaturates to yield arachidonic acid (C20:4n-6), the usual precursor of the eicosanoids of the dienoic or 2-double bond series.[10] The eicosanoids are the oxygenated products of arachidonic acid, including the prostaglandins synthesized by the cyclooxygenase pathway and the leukotrienes by the 5-lipoxygenase pathway (Fig. 2).

Another essential PUFA is alpha-linolenic acid (C18:3n-3), the parent fat of the n-3 PUFA eico-

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Table 1. The Beneficial Effects of n-3 PUFA in Cardiovascular and Autoimmune Diseases

Disease	Beneficial Effects
Coronary heart disease	Reduce the risk of death from cardiac and noncardiac causes in persons with [83,86,87] and without [82] a history of coronary heart disease
Hypertension	Improve blood pressure especially in hypertensive patients and those with clinical atherosclerotic disease or hypercholesterolemia [99]
Arrhythmias	Reduce risk of sudden cardiac death [83,84,86] by stabilizing the myocardium [83]
Stroke	Reduce the incidence of stroke [215]
Hypertriglyceridemia	Lower serum triglyceride levels [94]; fasting hypertriglyceridemia has been identified as an independent risk for ischemic heart disease [216]
End-stage renal disease	
Chronic dialysis patients	Decrease the risk of death from cardiovascular disease [86,87,95]; lower blood pressure in hypertensive patients [217]; prevent vascular access graft (PTFE) thrombosis [109]; reduce EPO requirements [218]; relieve uremic pruritis [219]
Transplant patients	Reduce cyclosporine-induced hypertension and renal function impairment in solid organ-transplanted patients receiving this drug for immunosuppression [220]; reduce rejection episodes and shorten hospitalizations in renal transplant recipients [221]
Rheumatoid arthritis	Ameliorate arthritic symptoms [222] and reduce nonsteroidal antiinflammatory drug therapy [223]
IgA nephropathy	Reduce renal disease progression in high-risk patients [1,2,6]

Abbreviations: PTFE, polytetrafluoroethylene (Teflon); EPO, erythropoietin.

sapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), which constitute the precursors for eicosanoids of the three-double bond series (Figs. 1 and 2). The first double bond from the methyl carbon atom end is at the third carbon atom, hence, the designation n-3 PUFA. Alpha-linolenic acid is found in the chloroplasts of green leafy vegetables, plant oils (canola, flaxseed, and soy), and nuts (walnut oil and walnuts). In mammals, once consumed, alpha-linolenic acid contained in these foods only slowly elongates and desaturates to EPA and DHA, making fish and marine oils the major and most convenient food sources of EPA and DHA (Table 2).

All fish contain EPA and DHA with the highest content found in herring, salmon, mackerel, sardines, trout, and tuna (Table 2). Body fat from many species of fish from cold water seas is purified and commercially processed to provide concentrated EPA and DHA n-3 PUFA in capsules or emulsified pouches (Table 2). Since the first n-3 PUFA advisory,[11] the U.S. Food and Drug Administration (FDA) has ruled that intakes of up to 3 g per day of marine n-3 PUFA are Generally Recognized As Safe (GRAS) for inclusion in the diet.[12] Also, the FDA recently has approved a qualified health claim for EPA and DHA n-3 PUFA in dietary supplements.[13]

The competitive rates of n-3 and n-6 PUFA in metabolism of PUFA[14] and their deficiencies in several human diseases have previously been reported.[15] EPA and DHA compete with arachidonic

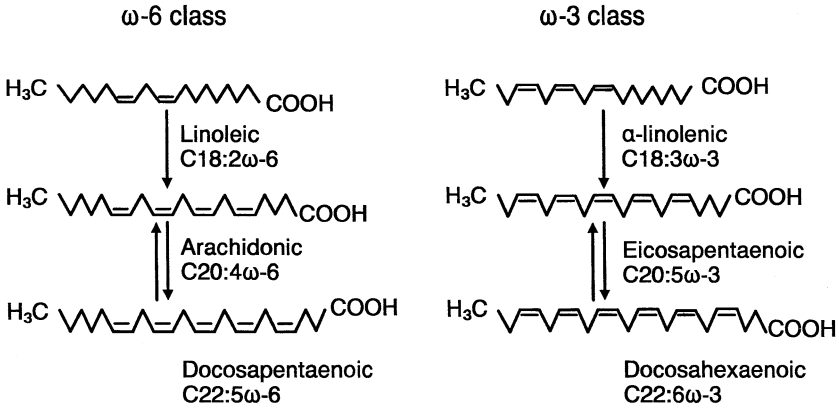

Fig 1. Diagram of the relationship of essential, long-chain polyunsaturated fatty acids (PUFA) of omega-6 (n-6) and omega-3 (n-3) classes. Transformations from parent PUFA, linoleic, and alpha-linolenic, shown by arrows, involve two or more reactions. Reprinted with permission from Donadio JV, Jr: Omega-3 polyunsaturated fatty acids: a potential new treatment of immune renal disease. Mayo Clin Proc 66: 1018–1028, 1991.[225]

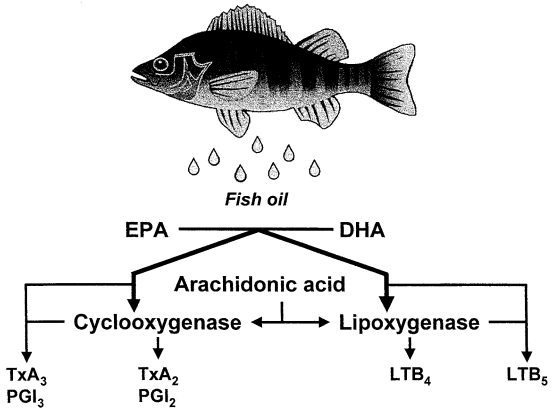

Fig 2. Cartoon representation of how n-3 PUFA, EPA and DHA, compete for cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism and shift the balance of eicosanoid metabolism from proinflammatory effects, for example, contraction of mesangial cells and induction of glomerular resident cell growth (thromboxane—A_2) and induction of adhesion of leukocytes (leukotriene—B_4), to antiinflammatory (thromboxane—A_3, leukotriene—B_5) and vasodilatory (prostaglandin—I_3) effects in glomerulonephritis. Reprinted with permission from Donadio JV: The emerging role of omega-3 polyunsaturated fatty acids in the management of patients with IgA nephropathy. J Ren Nutr 11:122–128, 2001.[226]

acid as substrate for cyclooxygenase for the two-position in membrane phospholipids and for elongase and desaturase enzymes, thereby reducing synthesis of arachidonic acid from linoleic acid (Figs. 1 and 2). Thus, the two families of EFA have small differences in structure yet are metabolically and functionally distinct and have opposing physiological features.

What is the ideal proportion of n-6 and n-3 fats in the diet? Today's Western diets have an n-6:n-3 fatty acid ratio of 10–20:1.[16] Based on the Lyon Diet Heart Study, the current recommended adequate intake for overall health indicates that a ratio of n-6:n-3 fats, for example, linoleic acid to alpha-linolenic acid, should approximate 4:1 or less.[17,18] Many investigators consider this change in the balance of n-6:n-3 fatty acid dietary intake important for changing the proportion of tissue PUFA to decrease excessive n-6 eicosanoid actions, for example, thromboxane-A_2-induced vasoconstriction and platelet aggregation and proinflammatory leukotrienes (Fig. 2).

Various organizations have made population-based dietary recommendations for n-3 PUFA typically in amounts of 0.3 to 0.5 g per day of EPA and DHA and 0.8 to 1.1 g per day of alpha-linolenic acid. Recently, the Food and Nutrition Board, Institute of Medicine, and The National Academies issued the Dietary Reference Intakes for Energy and Macronutrients.[19] The acceptable range for alpha-linolenic acid is estimated to be 0.6% to 1.2% of energy, or 1.3-2.7 g per day on the basis of a 2000 calorie diet. This is approximately 10 times the current intake of EPA and DHA in customary Western diets. The intent of these recommendations for n-3 PUFA is to provide guid-

Table 2. The Proximate Fatty Acid Composition of Fish Tissue and Fish Oils

Finfish Species*	EPA + DHA (g/3-oz serving)
Herring	
Pacific	1.81
Atlantic	1.71
Salmon	
Chinook	1.48
Pink	1.09
Sockeye	0.68
Atlantic, farmed	1.09–1.83
Atlantic, wild	0.9–1.56
Mackerel	0.34–1.57
Sardines	0.98–1.70
Trout, rainbow	
Farmed	0.98
Wild	0.84
Tuna	
Light, canned in water	0.26
White, canned in water	0.73
Fresh	0.24–1.28

Fish Oils	EPA + DHA g/g oil
Capsules	
Menhaden oil	0.29
Omega-3 fatty acid concentrates†	0.30
Omacor™‡	0.85
Emulsified pouches	
Coromega™§	0.58

Data from the USDA Nutrient Data Laboratory.[224]

* Partial listing of species.

† The most common over-the-counter fish oil capsules in the United States contain 0.18 g EPA and 0.12 g DHA.

‡ Manufactured by Pronova Biocare, Oslo, Norway, and not available in the United States.

§ Manufactured by European Reference Botanical Laboratories, Carlsbad, CA, available in orange-flavored pouches providing 0.35 g EPA and 0.23 g DHA.

ance for healthy people in contrast with the reported studies in chronic diseases (Table 1) in which both fish consumption and fish oil supplements, obviously in various amounts, were beneficial.

PATHOPHYSIOLOGY OF IgA NEPHROPATHY: POTENTIAL THERAPEUTIC TARGETS FOR n-3 PUFA

IgA nephropathy is defined by the presence of predominant or codominant deposits of IgA within the mesangial regions of glomeruli.[2,20] IgA deposition is associated with a wide variety of proliferative, inflammatory, and/or sclerosing lesions.[21] Clinical features associated with progressive renal disease in patients with IgA nephropathy include hypertension and proteinuria; histopathologic features associated with progressive disease include glomerular hypercellularity, the presence of interstitial inflammatory infiltrates, excessive matrix deposition, and vascular sclerosis.[21-24] Based on these considerations, n-3 PUFA could prevent renal disease progression by: (1) preventing glomerular deposition of immune complexes containing IgA1; (2) reducing blood pressure; (3) reducing urine protein excretion; (4) inhibiting vascular sclerosis; (5) inhibiting glomerular proliferation; (6) inhibiting inflammation; and/or (7) preventing excessive matrix deposition. In this section, recent advances in our understanding of the pathophysiology of IgA nephropathy are reviewed, with an emphasis on potential therapeutic targets of n-3 PUFA in preventing renal disease progression in patients with IgA nephropathy.

IgA NEPHROPATHY DEFINED BY MESANGIAL DEPOSITION OF IgA

Although the kidney is primarily affected, current evidence indicates that IgA nephropathy is a systemic disease. Of patients who receive renal allografts for treatment of end-stage renal disease (ESRD) resulting from IgA nephropathy, histologic evidence of recurrent disease is observed in up to 50%.[25-27] Some studies, of relatively small numbers of patients observed over brief periods of time, have indicated that recurrent IgA nephropathy is a benign condition.[26,28,29] However, more recent studies with longer patient follow up have suggested that recurrent IgA nephropathy produces significant loss of allograft function in 20% to 70% of affected patients.[30,31] On the other hand, mesangial IgA deposits in donor kidneys of patients with IgA nephropathy rapidly disappear when transplanted into recipients with ESRD as a result of causes other than IgA nephropathy.[32,33] These observations support the notion that extrarenal factors are responsible for the development and progression of IgA nephropathy.

Recent studies have suggested that abnormalities in IgA production, structure, and/or catabolism could facilitate renal deposition of immune complexes containing IgA, which is the defining feature of IgA nephropathy.[34] Some patients with IgA nephropathy have elevated serum levels of IgA or increased levels of IgA complexed to the FCα receptor (CD89) or to matrix macromolecules such as fibronectin.[35-40] No specific antigen has been consistently detected in circulating immune complexes containing IgA or in renal biopsy specimens from patients with IgA nephropathy.[41]

IgA nephropathy is characterized by mesangial deposition of polymeric IgA.[42] IgA production in response to immunization with tetanus toxoid is increased in patients with IgA nephropathy.[43] However, increased serum IgA levels are not sufficient to produce IgA nephropathy. For example, patients with IgA-secreting multiple myeloma or with AIDS have increased serum IgA levels but typically do not develop IgA nephropathy.[44-46]

IgA nephropathy is frequently associated with upper respiratory tract infections, prompting speculation that this disease is associated with hyperactivity of the mucosal immune system.[47,48] Permeability of the gastrointestinal mucosa is increased in patients with IgA nephropathy, and intestinal permeability seems to correlate with serum IgA levels.[49] However, current evidence indicates that mucosal immunity, which is in part directed by IgA, is decreased in patients with IgA nephropathy.[50] Expression of the Vγ3 and Vδ3 genes are decreased in cells isolated from both the bone marrow and duodenal mucosa of patients with IgA nephropathy compared with normal controls.[42,51] γ/δ T cells regulate mucosal IgA production and oral tolerance. This apparent defect in cell immunity does not produce any apparent clinical symptoms. However, polymeric IgA production by the mucosal immune system is decreased in patients with IgA nephropathy, whereas polymeric IgA production in the bone marrow is increased.[34,39,40,42,52,53] It is not clear how the decreased mucosal and increased systemic polymeric

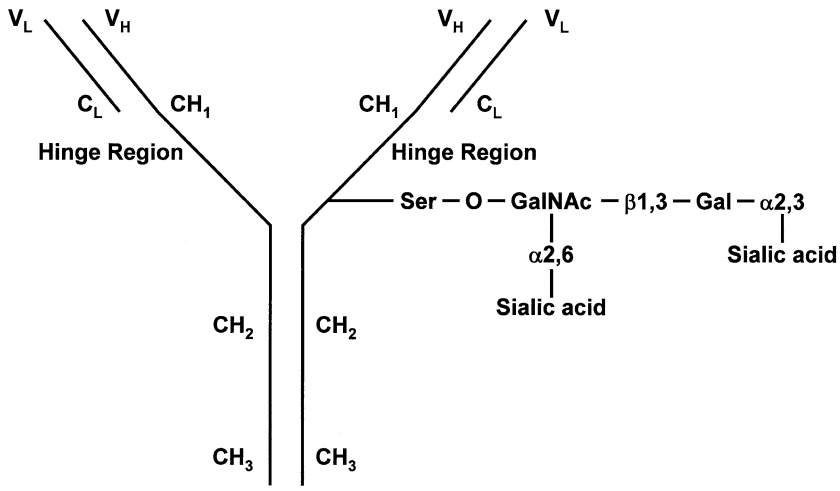

Fig 3. Structure of normal IgA1. The hinge region contains multiple serine residues, which provide sites for O-linked glycosylation. N-acetyl-galactosamine (GalNAc) is O-linked to serine residues within the hinge region. Galactose is added to the GalNAc residues through a β1,3 link. Sialic acid is attached to galactose or GalNAc through α2,3 and α2,6 links, respectively. In IgA nephropathy, the number of galactose residues attached to GalNAc appears to be reduced.

IgA production or decreased Vγ3-Vδ3 expression by T cells at both sites contribute to the pathogenesis of IgA nephropathy.

Although humans produce two isotypes of IgA, IgA1 and IgA2, the glomerular deposits of IgA in IgA nephropathy contain exclusively IgA1.[37,54] Plasma cells associated with the gastrointestinal and respiratory tract produce both IgA1 and IgA2, whereas plasma cells in bone marrow, lymph nodes, and spleen produce predominantly IgA1.[54] A unique feature of IgA1 is the presence of multiple O-linked ligands in the hinge region between the CH1 and CH2 domains of the immunoglobulin heavy chain.[55] IgA2 and other immunoglobulins do not possess O-linked ligands. Each of the O-linked ligands consists of N-acetyl-galactosamine (GalNAc) O-linked to serine residues. Although O-glycosylation of threonine residues (four of which are present in the hinge region of IgA1) is possible, this has not been described in IgA1 (Fig. 3). The glycan chains are elongated with addition of galactose (Gal) in β1,3 linkage with GalNAc and a variable degree of sialylation.[56] The lectin vicia villosa (VV), which recognizes O-linked GalNAc, shows higher binding to IgA1 from patients with IgA nephropathy than control subjects.[57,58] This finding suggests that the galactosylation of GalNAc moieties is reduced in patients with IgA nephropathy, resulting in increased exposure of GalNAc to lectin binding.[53] IgA1 isolated from serum of patients with IgA nephropathy shows a defect in galactosylation.[44,59] A recent study has shown an identical defect in galactosylation of IgA1 eluted from renal tissue of patients with IgA nephropathy.[60] The nucleotide sequence of the IgA hinge region is normal in patients with IgA nephropathy, suggesting that the decreased galactosylation occurs through posttranslational mechanisms.[55]

The galactose residues are added to GalNAc through activity of the enzyme β1,3 galactosyl transferase. Activity of β1,3 galactosyl transferase is decreased in B cells isolated from patients with IgA nephropathy compared with normal control subjects.[53,61] β1,3 galactosyl transferase activity of lysates obtained from T cells and monocytes do not differ between IgA nephropathy patients and control subjects.[61]

Abnormalities in cellular immunity have been detected in patients with IgA nephropathy. In particular, increased production of the TH_2 cytokines IL-4 (which promotes immunoglobulin class switching) and IL-5 (which promotes differentiation of IgA-bearing B lymphocytes) has been noted in patients with IgA nephropathy.[62-65] Treatment of murine B cells with IL-4 and IL-5 alters glycosylation of IgA. In particular, increased numbers of terminal sialic acid residues on IgA were noted.[66] Increased sialylation of polymeric IgA has been recently demonstrated in patients with IgA nephropathy.[67] In a murine model of IgA nephropathy induced by oral challenge with Sendai virus, increased production of the Th_2 cytokines IL-4 and IL-5 was observed in splenocytes.[68] Th_2 cytokine production was associated with a significant decrease in galactosylation and terminal sialylation of Sendai virus-specific IgA1. This glycosylation defect induced by Th_2 cytokines *in vitro* could be

reversed by administration of IFNα.[68] These studies indicate that glycosylation of IgA could in part be regulated by cytokines.

Recent evidence indicates that the galactosylation defect in patients with IgA nephropathy is associated with reduced clearance and increased renal deposition of IgA1. IgA1 isolated from patients with IgA nephropathy and injected into mice survives longer in the circulation than IgA1 isolated from healthy controls.[69,70] A major pathway for clearance of circulating IgA1 is through the hepatic asialoglycoprotein receptor.[44,71,72] This receptor recognizes galactose residues within the hinge region of IgA1.[71,72] It remains to be determined whether hepatic clearance of abnormally glycosylated IgA1 is decreased in patients with IgA nephropathy.[50]

Although many studies have demonstrated that mesangial cells (MC) bind IgA, the nature of the putative receptor on MC has not been adequately defined. Both the FCα receptor (CD89) and the transferrin receptor have been implicated in mesangial IgA deposition.[73,74] It is possible that undergalactosylated IgA has increased affinity for IgA-binding sites on MC. In support of this notion, binding of IgA1 obtained from normal individuals shows increased binding to human MC after it is treated with β galactosidase to remove galactose residues.[70]

Once deposited in the kidney, IgA1-containing immune complexes trigger proliferative, inflammatory, and matrix signaling pathways.[75,76] In humans, there is no evidence that n-3 PUFA decrease production of IgA1, increase the galactosylation of IgA1, or increase clearance of IgA1. It is likely that n-3 PUFA prevent renal disease progression in patients with IgA nephropathy by interfering with effector pathways triggered by mesangial immune complex deposition. Insights from animal models of mesangial injury independent of IgA nephropathy, particularly the Thy 1 model of mesangial proliferative glomerulonephritis, have emphasized the cascades of growth factors and cytokines involved in MC injury and repair. For example, platelet-derived growth factor has been implicated in the proliferation of MC in patients with IgA nephropathy and a variety of other glomerular diseases.[77,78] Transforming growth factor β1 (TGF-β1) has emerged as a predominant fibrogenic cytokine, which leads to glomerulosclerosis, interstitial fibrosis, and tubular atrophy.[79,80] Renal localization of TGF-β1 correlates with the severity of tubulointerstitial damage in patients with IgA nephropathy.[81] Most of the currently used therapies for IgA nephropathy are directed at these nonimmune complex-mediated mechanisms of renal disease progression. Clinical markers of disease progression, including hypertension and proteinuria, are common to all forms of chronic renal disease. Histopathologic markers of chronic injury, including glomerulosclerosis, interstitial fibrosis, and tubular atrophy, are also common to all forms of progressive renal disease. In the next sections, potential targets of n-3 PUFA relevant to renal disease progression in patients with IgA nephropathy are discussed.

n-3 PUFA PROTECT AGAINST THE DEVELOPMENT AND PROGRESSION OF CARDIOVASCULAR DISEASE

Recent studies have shown that individuals who regularly consume n-3 PUFA are at lower risk for the development of sudden cardiac death.[11,82-85] In patients who have survived a myocardial infarction, dietary n-3 PUFA supplementation reduces the risk of death, nonfatal myocardial infarction, and stroke.[86] In an angiographic study, reduced progression of coronary artery disease is observed in patients who regularly took n-3 PUFA.[87] Serum levels of the acute phase reactant c-reactive protein, which is an independent risk factor for subsequent development of coronary artery disease, are inversely correlated with granulocyte membrane content of DHA.[88] n-3 PUFA reduce the susceptibility of myocardial tissue to the development of ventricular arrhythmias.[89-91]

n-3 PUFA could prevent the development and progression of cardiovascular disease by decreasing serum lipid levels, reducing blood pressure, decreasing vascular reactivity, or preventing thrombosis. It is possible that the progression of IgA nephropathy could be prevented by n-3 PUFA through similar pathways.

n-3 PUFA REDUCE SERUM LIPID LEVELS

It is well recognized that increased triglyceride levels are a risk factor for the development of both cardiovascular disease and the progression of IgA nephropathy.[92,93] n-3 PUFA significantly reduce triglyceride levels, with lesser effects on cholesterol or low-density lipoprotein levels.[94-97] The triglyceride-

lowering effect of n-3 PUFA is associated with an increase in lipoprotein lipase activity.[98]

n-3 PUFA REDUCE BLOOD PRESSURE

Elevated blood pressure is a strong risk factor for the development of progressive renal disease in patients with IgA nephropathy.[22] In two meta-analyses of randomized trials, n-3 PUFA significantly decrease both systolic and diastolic blood pressure.[99,100] n-3 PUFA prevent the development of hypertension and renal damage in stroke-prone spontaneously hypertensive rats.[101-103] In isolated aorta from spontaneously hypertensive rats, n-3 PUFA promote vasorelaxation through modulation of intracellular calcium release.[104-106] In hyperlipidemic individuals, n-3 PUFA increase systemic arterial compliance.[107] DHA, a component of fish oil, enhances vasodilatory responses to nitric oxide donors and attenuates vasoconstrictor responses to norepinephrine in forearm vessels of human subjects.[108]

n-3 PUFA AND OTHER EFFECTS

Recent studies have shown that n-3 PUFA dramatically reduce the incidence of polytetrafluoroethylene graft thrombosis in dialysis patients.[109] n-3 PUFA inhibit platelet aggregation through inhibition of thromboxane A_2 synthesis and through inhibition of platelet-activating factor production.[110-113] n-3 PUFA decrease platelet aggregation.[112,113] n-3 PUFA suppress adhesion of monocytes to endothelial cells[114,115] and reduces expression of adhesion molecules on endothelial cells and leukocytes.[116-118]

n-3 PUFA AND PROTEINURIA

Proteinuria has emerged as a strong risk factor for renal disease progression in patients with IgA nephropathy.[22] In several experimental models of renal injury, n-3 PUFA reduce proteinuria.[119-123] High-dose n-3 PUFA therapy reduces proteinuria in patients with chronic glomerular diseases, including focal-segmental glomerulosclerosis and membranous nephropathy.[124] However, randomized, controlled studies have failed to demonstrate a consistent reduction in urine protein excretion in patients with IgA nephropathy.[1,2,6,125]

n-3 PUFA INTERFERE WITH EICOSANOID METABOLISM

Arachidonic acid is metabolized through the cyclooxygenase or lipoxygenase pathways to produce a wide variety of inflammatory mediators. The n-3 PUFA EPA can replace arachidonic acid in phospholipids bilayers and serve as a competitive inhibitor of cyclooxygenase, leading to decreased production of thromboxane A_2, prostaglandin PGI_2, and leukotrienes C_4, D_4, and E_4.[126] EPA is a substrate for the production of thromboxane A_3, PGI_3, and leukotrienes B_5, C_5, and D_5.[127,128] Cyclooxygenase and lipoxygenase products produced from EPA are much less potent as inflammatory mediators than are products generated from arachidonic acid. Although the n-3 PUFA DHA does not directly inhibit arachidonic acid metabolism, DHA inhibits platelet aggregation by reducing affinity of platelet thromboxane A_2/prostaglandin H_2 receptor for its ligand.[129] In the kidney, thromboxane A_2 promotes intense vasoconstriction and MC contraction.[130,131] Increased production of cyclooxygenase and lipoxygenase pathway products have been identified in patients with IgA nephropathy.[132,133] The beneficial effects of n-3 PUFA could be increased by concomitant administration of aspirin.[134] N-3 PUFA could also suppress inflammatory and/or immunologic responses through eicosanoid-independent mechanisms.[135]

PROLIFERATION

N-3 PUFA inhibit cell growth in response to a variety of growth factors, including PDGF, endothelin-1, thromboxane A_2, and serotonin.[136-140] The n-6 PUFA oleic acid or linoleic acid do not inhibit mitogenesis.[122,141,142] In vascular smooth muscle cells and a variety of transformed cell lines, the growth inhibitory effect of n-3 PUFA is associated with induction of apoptosis.[143-146] However, DHA inhibits apoptosis in peripheral blood myeloid cells and neurons.[147-149] In mesangial cells, both of the n-3 PUFA DHA and EPA are readily incorporated into plasma membranes and tend to replace arachidonic acid as a plasma membrane constituent.[122]

Potential cell cycle targets underlying the antiproliferative effect of DHA or EPA are outlined in Figure 4. At a dose of 10 to 20 μM/L, DHA, but not EPA, inhibits proliferation of MC[122] without triggering apoptosis. At higher doses (100 μM/L), both EPA and DHA inhibit MC proliferation. Other investigators have demonstrated that the higher doses of EPA are effective in suppressing the proliferation of MC.[136]

In a recent study, the differential effect of DHA versus EPA on MC mitogenesis was found to be

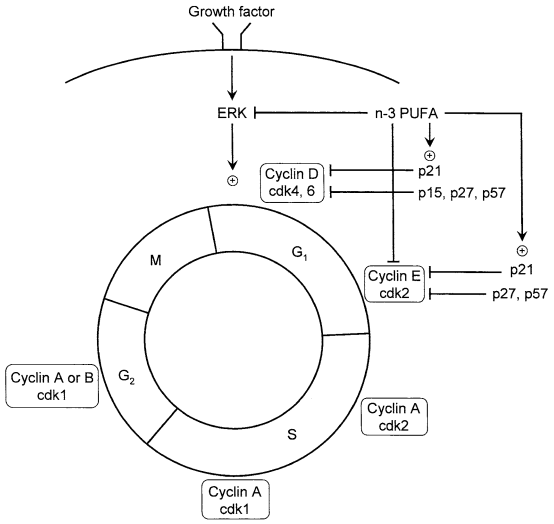

Fig 4. Potential mechanisms by which n-3 PUFA inhibit MC mitogenesis. n-3 PUFA inhibit growth factor-stimulated ERK activation, decrease cyclin E kinase activity, and induce the cell cycle inhibitor p21. See text for details.

associated with differential regulation of MAPK-signaling pathways.[150] MAPK are key regulators of cell growth and apoptosis and include ERK, p38, and JNK.[151,152] At a dose of 20 μM/L, DHA, but not EPA, decreased ERK activation. JNK activity was increased by DHA, but not EPA. DHA and EPA did not significantly alter p38 activity.[150]

Mitogenesis is regulated through sequential activation of a series of cyclin–cyclin-dependent kinase complexes.[153-156] A major point of regulation of the cell cycle is in the G1 to S transition. When a cell is stimulated to proliferate, cyclin D associates with the cyclin-dependent kinases cdk4 and cdk6, whereas cyclin E associates with cdk2. Both cyclin D-cdk4/cdk6 and cyclin E-cdk2 phosphorylate the retinoblastoma protein (pRb).[157,158] Activation of both cyclin D and cyclin E are essential for progression from the G1 phase to the S phase of the cell cycle.[154,159] In MC, DHA reduces cyclin E activity, as assessed by histone H1 kinase assay.[150] DHA has no effect on cyclin D levels or cyclin D activity, cyclin E levels, or cdk levels. In vascular SMC, higher doses of both EPA and DHA inhibit proliferation by blocking phosphorylation of the cyclin E-cdk2 complex.[160] In colon cancer cells, DHA inhibits proliferation by preventing activation of both cyclin D and cyclin E.[161] In leukemic K-562 cells, EPA downregulates cyclin E expression.[162]

Activity of cyclin–cdk complexes is regulated by two families of cdk inhibitory proteins: the INK family, which includes p15, p16, p18, and p19; and the Kip family, which includes p21, p27, and p57.[163] The INK family of cdk inhibitors preferentially bind cdk4 or cdk6, whereas the Kip family blocks activity of a variety of cyclin–cdk complexes, including that of cyclin E-cdk2.[164] The antiproliferative effect of DHA is associated with induction of the cell cycle inhibitor p21; EPA has no significant effect on p21 levels.[150] DHA and EPA do not alter p27 levels. Further studies are needed to define the *in vivo* relevance of these findings in patients with IgA nephropathy.

n-3 PUFA INHIBIT RENAL INFLAMMATION

Progression of renal disease in patients with IgA nephropathy is associated with glomerular and interstitial inflammation.[22] It is well recognized that progression of IgA nephropathy is associated with production of a variety of proinflammatory cytokines.[75,165-167] Increased production of Th1 cytokines (γ-interferon) is associated with renal dysfunction in patients with IgA nephropathy.[166,168-170] Elevated blood γ-interferon levels correlate with increased proliferative activity in renal biopsy tissue, as assessed by Ki-67 expression.[171] Some studies indicate that n-3 PUFA downregulate Th1 type responses.[172]

Production of proinflammatory cytokines (TNF, IL-1) correlate with proteinuria in patients with IgA nephropathy.[168] n-3 PUFA inhibit the production of IL-1 and TNF by circulating leukocytes.[173-175] Production of TNF and other proinflammatory cytokines occurs through the NF-κB signaling pathway. In resting cells, NF-κB is rendered inactive through binding to IκB. After appropriate stimulation, IκB is phosphorylated, causing it to dissociate from NF-κB, leading to activation of the NF-κB signaling pathway. In monocytes, n-3 PUFA suppress TNF production by inhibiting IκB phosphorylation, preventing the activation of NF-κB.[176]

In cultured MC, IL-6, and other proinflammatory cytokines induce FCα receptor mRNA expression. This interaction of FCα receptors and IgA on MC activates the NF-κB signaling pathway and stimulates the production of other cytokines, including IL-8 and MCP-1.[177,178] Immune complexes containing IgA lead to secretion by MC of IL-1, IL-6, and platelet-activating factor.[75] IL-6 stimu-

Table 3. Fish-Oil Treatment of Patients With IgA Nephropathy Reported in Randomized Clinical Trials

	Trial Conditions		
Geographic Location	EPA/DHA (g/day)	Duration of Treatment (yr)	Renal Function Outcome
Japan[3] (n = 20)	1.6/1.0	1	Stabilized
Australia[4] (n = 37)	1.8/1.2	2	Declined
Sweden[5] (n = 32)	3.3/1.8	0.5	Declined
North America[1] (n = 106)	1.8/1.2	2	Stabilized

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Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

lates proliferation of MC and matrix synthesis. IL-6 expression positively correlates with pathologic score and prognosis of patients with IgA nephropathy.[78,179] Increased urine IL-6 levels correlate with the degree of histologic damage in patients with IgA nephropathy.[179-181] n-3 PUFA inhibit endothelial cell production of IL-6.[182] The role of n-3 PUFA on renal IL-6 production has not yet been established. n-3 PUFA also inhibit the production of other proinflammatory cytokines, including endothelin-1,[137] nitric oxide,[183,184] and platelet-activating factor.[185] In vitro, n-3 PUFA decrease production of platelet-derived growth factor, a factor that has been shown to play an important role in initiating mitogenic signaling pathways by MC in patients with IgA nephropathy.[186-188]

In Vivo Studies

MC proliferation is a characteristic feature of IgA nephropathy. The Thy 1 glomerulonephritis model has been widely used to study signaling pathways underlying mesangial proliferative glomerulonephritis and to test therapeutic efficacy of a variety of agents in preventing acute renal damage. In this model, rats are treated with monoclonal or polyclonal antibodies to the Thy 1 antigen, which is expressed on MC. After antibody administration, an initial complement-dependent mesangiolysis is followed by proliferation of MC.[189,190] The proliferating MC acquire a "myofibroblast" phenotype characterized by *de novo* expression of α smooth muscle actin.[191] These alterations are associated with influx of macrophages into glomeruli[190] and deposition of extracellular matrix.[190] Similar histopathologic alterations have been identified in IgA nephropathy and other mesangial proliferative glomerular diseases.[191-193] Although the Thy 1 model does not involve glomerular deposition of IgA, it is hypothesized that the mitogenic, inflammatory, and matrix-signaling pathways stimulated in this model are similar to those described in patients with IgA nephropathy.

In a recent study, rats were treated with fish oil (4.7 g/kg EPA and 3.7 g/kg DHA per day) before induction of Thy 1 glomerulonephritis.[122] At this dose, the n-3 PUFA were readily incorporated into plasma and renal tissue phospholipids. After induction of Thy 1 glomerulonephritis, urine protein excretion was decreased by over 50% in animals treated with n-3 PUFA as compared with sesame oil-treated controls. n-3 PUFA treatment reduced glomerular proliferation by 50% (as assessed by PCNA staining), glomerular α smooth muscle actin expression by 27% (as assessed by semiquantitative analysis of immunohistochemical stains), and histologic manifestations of glomerular injury by 40% (as assessed by semiquantitative scoring of periodic acid Schiff-stained sections). This study indicates that n-3 PUFA are effective in reducing the proliferative response to acute injury in this model. It remains to be determined whether n-3 PUFA are capable of preventing the development or progression of renal injury in a chronic Thy 1 model. In susceptible mice, prolonged dietary exposure to vomitoxin induces elevated serum IgA levels and mesangial IgA deposition.[194-196] In this model, n-3 PUFA supplementation reduced serum IgA levels and decreased mesangial IgA deposition.[197]

CLINICAL STUDIES, DOSE RECOMMENDATIONS, AND SAFETY THAT SUPPORT THE USE OF N-3 PUFA IN IgA NEPHROPATHY

Efficacy of n-3 PUFA in the treatment of patients with IgA nephropathy has been tested using

dietary fish oil supplements in four randomized clinical trials (Table 3). Results varied with two studies showing that treatment stabilized renal function,[1,3] whereas two reported a decline in renal function.[4,5] Potential reasons for these discordant results include the relatively small number of patients enrolled in three of the four studies, the short duration of treatment in two studies, i.e., 1 year or less, and the failure to control for risks known to be associated with progressive renal disease such as hypertension, proteinuria, and impaired renal function at diagnosis. Importantly, the majority of the patients in the four trials were adults with chronic, slowly progressive disease, the most common clinical course of patients with IgA nephropathy.[198]

A metaanalysis of these four randomized trials plus a small, nonrandomized study showed that the probability of at least a minor beneficial effect on the preservation of renal function was 75%.[199]

The largest study performed by our collaborative group[1] was a randomized, placebo-controlled trial in patients with persistent proteinuria (exceeding 1 g per 24 hours) and impaired renal function (serum creatinine levels up to 3.0 mg/dL) at study entry. That study provided strong evidence that treatment for 2 years with a daily dose of 1.8 g EPA and 1.2 g DHA reduced the risk of a 50% increase in the serum creatinine concentration by 82%. Treatment also lowered the risk of death or end-stage renal disease by 67%. The annualized median change in creatinine clearance was stable with an increase of only 0.3 mL/min/1.73 m^2 (body surface area) in patients treated with fish oil, as compared with a decrease of 7.1 ml/min/1.73 m^2 in patients who received placebo (Fig. 5). In addition, 11 of 55 (20%) patients who received fish oil had substantial improvement in their renal function, i.e., showed an increase in creatinine clearance of 20% or more, compared with 5 of 51 (10%) patients who were given placebo over the 2-year study period.

In a follow-up study of this cohort of patients, those who chose to remain on fish oil after the 2-year study period continued to have better maintained renal function than those that never received fish oil.[2] After a mean follow-up period of 6.4 years, 29 patients in the original placebo group had reached the primary end point (an increase of 50% or more in serum creatinine) versus 17 in the original fish oil group (Fig. 6). Nineteen patients in the placebo group developed end-stage renal disease compared with only 8 in the fish oil group (Fig. 7).

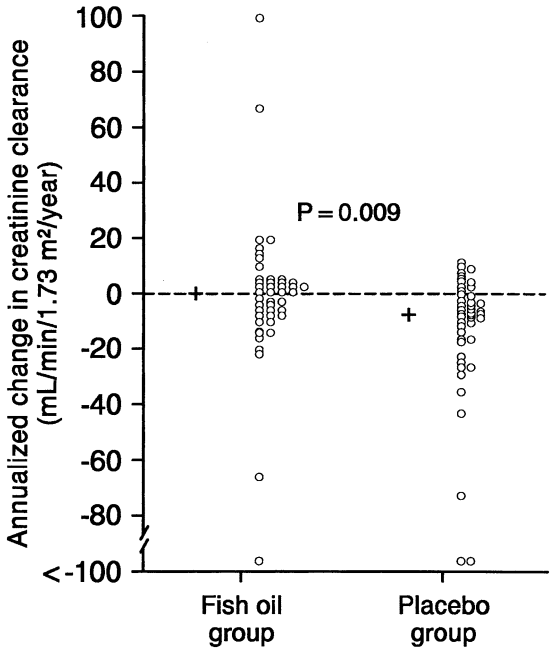

Fig 5. Annualized rate of change in creatinine clearance in patients with IgA nephropathy treated with fish oil or placebo. The annualized median change in creatinine clearance was –0.3 mL/min/1.73 m^2 in the fish oil group and –7.1 mL/min/1.73 m^2 in the placebo group. Zero represents no change; the median values are indicated by + signs. Reprinted with permission from Donadio JV, Bergstralh EJ, Offord KP, et al: A controlled of fish oil in IgA nephropathy. N Engl J Med 331:1194–1199, 1994.[1] ***©1994 Massachusetts Medical Society. All rights reserved.***

In a recent open-label, parallel group study, the protective effect on renal function of fish oil was similar in 73 high-risk patients with IgA nephropathy receiving either high-dose fatty acids (EPA 3.76 g per day plus DHA 2.94 g per day) or "standard-dose" fatty acids (EPA 1.88 g per day plus DHA 1.47 g per day) for a minimum of 2 years.[6] We believe it is appropriate to recommend this "standard dose" of n-3 PUFA in the treatment of high-risk patients, including those with moderately advanced renal disease, i.e., in those patients in whom serum creatinine levels are less than 3.0 mg/dL and urinary protein excretion is greater than 0.5 g per 24 hours.

In all of the randomized trials using n-3 PUFA, there was an inconsistent reduction in proteinuria,[1-6] raising concerns about the long-term efficacy of n-3 PUFA.[200] In our first study,[1,2] despite

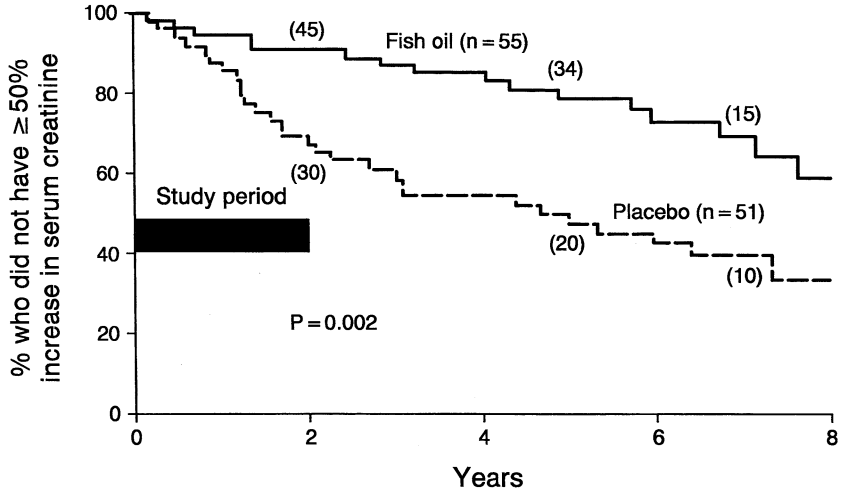

Fig 6. Cumulative percentage of patients with IgA nephropathy treated with fish oil or placebo whose serum creatinine did not increase by 50% or more to last follow up. Forty-four patients in the original fish oil group and 17 patients in the original placebo group received fish oil from year 2 onward and were at risk for the primary end point at the end of the 2-year trial. Thirteen at-risk patients in the original placebo group did not take fish oil for the duration of their follow up (n = number of patients at risk). Risk reduction, i.e., the percent change in cumulative risk for using drug over placebo, was 0.46, or 46%. Reprinted with permission from Donadio J, Grande J, Bergstralh E, et al: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. J Am Soc Nephrol 10:1772–1777, 1999.[2]

the differences in renal end points favoring the fish oil-treated group, the overall reduction in proteinuria was modest and not significantly different between the fish oil and placebo groups, nor between normotensive and hypertensive patients, the latter having been treated primarily with an angiotensin-converting enzyme inhibitor (ACEi). However, the magnitude of the reduction in urine protein was similar to that achieved in studies reporting the effects of ACEi in patients with IgA nephropathy,[201-204] the majority of whom had urine protein levels in the subnephrotic range, i.e., between 1.0 and 3.0 g per 24 hours, as was the case with our patients. In our second trial, the open-label, two-dose comparative study,[6] there was also a modest decline in proteinuria and evidence of a slowing in the rate of renal function loss in high-risk patients with moderately advanced disease.

We previously determined that a dose of n-3 PUFA, composed of 1.8 g to 1.9 g EPA and 1.2 g

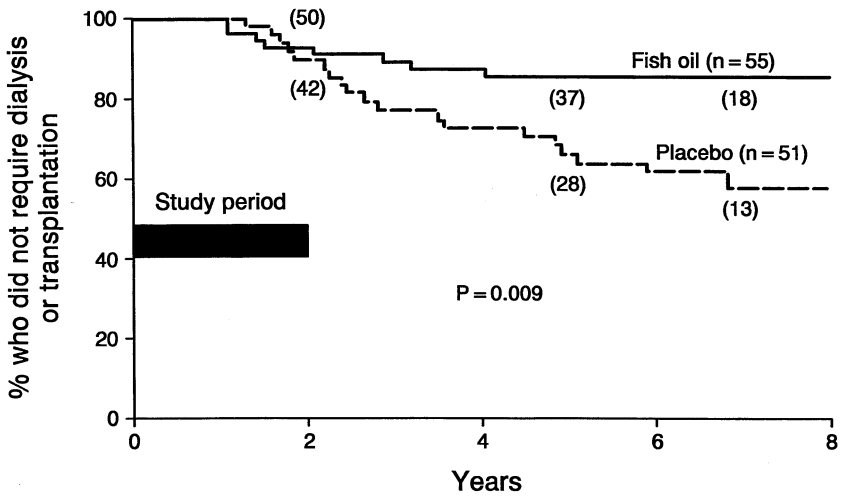

Fig 7. Cumulative percentage of patients with IgA nephropathy treated with fish oil or placebo who did not develop end-stage renal disease to last follow up (n = number of patients at risk. Risk reduction = 0.61 (61%). Reprinted with permission from Donadio J, Grande J, Bergstralh E, et al: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial.J Am Soc Nephrol 10:1772–1777, 1999.[2]

to 1.4 g DHA, efficiently enhanced the EPA and DHA and total n-3 PUFA of plasma phospholipids in patients with IgA nephropathy,[1,6,205] strengthening our recommendation for this dose of n-3 PUFA that is based primarily on the beneficial results of slowing progressive renal disease obtained in our clinical trials.[1,2,6]

The safety and content of dietary supplements of EPA and DHA n-3 PUFA has recently been reviewed.[83] The usual fish oil supplements available over-the-counter in pharmacies and health food stores are not standardized by refinement, content, or encapsulation procedures. One does not know what they contain in the way of contaminants or oxidation products. We can recommend two products that are pharmaceutical-grade fish oil concentrates, Omacor (Pronova Biocare, Oslo, Norway) and Coromega (European Reference Botanical Laboratories, Carlsbad, CA). Pronova Biocare provides the fish oil used in Omacor capsules and Coromega emulsified pouches. Omacor is not available in the United States. Coromega is manufactured in a pharmaceutically qualified facility in Carlsbad, California, using the highest quality ingredients and pharmaceutical Good Manufacturing Procedures. The oil is produced from raw fish oil through a three-stage process of purification and concentration that complies with European standards of Good Manufacturing Practice.[206] This process yields oils that are highly refined and therefore represent a pharmaceutical preparation in which potential impurities such as polychlorinated biphenyls, heavy metals, and dioxins are effectively removed, as are pesticide residues, unwanted fatty acids, and oxidation products.

Also, the convenience of n-3 fatty acid dosing with these products is at issue. The most common over-the-counter fish oil capsules in the United States contain 0.18 g of EPA and 0.12 g of DHA per capsule. Each Omacor capsule provides 0.47 g of EPA and 0.37 g of DHA, and each Coromega pouch provides 0.35 g of EPA and 0.23 g of DHA. Patients with IgA nephropathy must consume 10 to 12 over-the-counter fish oil capsules compared with 4 Omacor capsules or 5 Coromega pouches each day to achieve the current recommended dose of n-3 PUFA.

As mentioned, no clinical trials have been undertaken in IgA nephropathy using fish as the source of n-3 PUFA.

Some mild side effects occur with n-3 fatty acid supplements.[83] The most common side effect is a fishy aftertaste followed by gastrointestinal intolerance. In our two trials that involved the prospective study of 179 patients,[1,6] only two patients discontinued treatment as a result of gastrointestinal intolerance: one patient experiencing indigestion after taking fish oil for 18 months that resolved promptly after stopping the supplement, and a second patient, with a history of Barrett's esophagus, discontinuing medication 6 weeks after study entry as a result of an exacerbation of reflux esophagitis. In neither of the two trials did we observe unfavorable effects on hemostasis, lipid profiles, hematocrits, peripheral blood leukocytes, or platelets.

FUTURE DIRECTIONS

Although n-3 PUFA are potent inhibitors of inflammation *in vivo*[17] and of leukocyte function *in vitro*,[207] recent studies have shown that n-3 PUFA stimulate the neutrophil respiratory burst.[208,209] This proinflammatory effect of n-3 PUFA may be responsible for the modest clinical efficacy of these agents in treating a variety of diseases, including rheumatoid arthritis,[210] multiple sclerosis,[211] insulin-dependent diabetes,[212] psoriasis, atopic dermatitis,[213] and perhaps IgA nephropathy. In recent studies, chemically modified derivatives of n-3 PUFA (hydroperoxy PUFA or β-hydroxy PUFA) have been shown to be more potent than n-3 PUFA in suppressing activation of macrophages, T cells, and endothelial cells[208,214] without stimulating the neutrophil respiratory burst.[209] In particular, the β-hydroxy PUFA inhibit cytokine-stimulated T lymphocyte proliferation and production of TNF-β, IFN-γ, and IL-2 suppressed delayed-type hypersensitivity responses and edema in an *in vivo* model. Inhibition of these inflammatory responses was associated with decreased activation of protein kinase C, inhibition of ERK, but not JNK or p38.[209] Further studies are needed to determine whether these modified n-3 PUFA will have increased therapeutic efficacy in treating IgA nephropathy or other chronic inflammatory diseases.

ADDENDUM

Two additional randomized, controlled clinical trials testing efficacy of n-3 PUFA, published in abstract form, had different results; one showed preservation of renal function and reduction in proteinuria (J Am Soc Nephrol 12:89A, 2001), and one showed no effect on reducing progression of renal disease (J Am Soc Nephrol 14:751A, 2003).

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