

Review of the Effects of Omega-3 Supplementation in Dialysis Patients

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Chronic dialysis patients experience a host of conditions that limit quality and length of life, and recent therapeutic strategies have had only modest success in ameliorating many of these problems. By mediating cell membrane function and structure and the synthesis of lipid mediators such as eicosanoids, omega-3 fatty acids may offer dialysis patients a host of therapeutic benefits. Omega-3 fatty acids are derived primarily from dietary sources, and cold-water fish is the main source of eicosapentanoic and docosahexanoic acids, the two major bioactive omega-3 fatty acids. Studies of omega-3 supplementation in dialysis patients describe salutary effects on triglyceride levels, dialysis access patency, and perhaps uremic pruritus and oxidative stress. In contrast, the putative hematologic, antihypertensive, anti-inflammatory, and antiarrhythmic effects are not as well documented. Adverse effects generally have been limited to gastrointestinal complaints. Unfortunately, the preponderance of published studies are characterized by suboptimal study design, small sample sizes, supraphysiologic omega-3 doses that may be difficult to consume for extended periods, little long-term follow-up, and a lack of confirmation of compliance. Not surprising, the 2005 National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommend further research in this field. In summary, although preliminary data suggest that omega-3 fatty acids may have clinical benefits, formal recommendations encouraging omega-3 supplementation of dialysis patients are premature until long-term and adverse effects are better defined.

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The ESRD population is vulnerable to a host of often unique complications and comorbid conditions that adversely affect quality and length of life. Among these are metabolic derangements, hypertension, dialysis access malfunction, uremia-related pruritus, and exceptionally high mortality rates from cardiovascular and other causes. Unfortunately, novel dialysis and pharmacologic strategies introduced over the past decade have had only limited success in improving many of these outcomes (1,2). This fact highlights the need to identify more effective therapies.

By modulating cell membrane structure and function as well as synthesis of lipid mediators such as eicosanoids, omega-3 fatty acid supplementation may offer multiple health benefits to dialysis patients. Omega-3 fatty acids have shown promise in the general population in modifying a host of disease processes involving the inflammatory and immune pathways, arteriosclerosis and cardiovascular disease, cardiac dysrhythmias, rheology, and BP and lipid regulation, among others (3–8). Despite the potential for diverse clinical applications, omega-3 supplementation is neither routinely recommended nor used in the dialysis-dependent population. This is probably related in part to a general lack of familiarity with the biochemical and clinical effects of omega-3 therapy. This may soon change, as the 2005

National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommend further investigation in this area (9).

The purpose of this article is to review in a comprehensive manner the body of literature on omega-3 supplementation in dialysis patients. It briefly discusses the determinants, status, and biology of omega-3 fatty acids in healthy individuals and dialysis patients and then examines in greater detail the clinical and biologic effects of omega-3 supplementation in the dialysis population.

Published omega-3 data in dialysis patients were identified through a literature review conducted in July 2005 that used the Medline database. The few studies in languages other than English were not included. The search used key words related to dialysis (kidney failure, chronic renal failure, dialysis, hemodialysis, peritoneal dialysis) and omega-3 fatty acids (fatty acid, omega 3, fish oil, α -linolenic acid, eicosapentanoic acid, docosahexanoic acid). Articles that were retrieved were examined for additional references.

Omega-3 Determinants, Status, and Intake in Healthy Individuals

Omega-3 fatty acids are a family of fatty acids that contain two or more double bonds (“polyunsaturated”), one of which is located three carbon positions from the methyl terminus (“omega-3” or “n-3”). Because the body is unable to synthesize in appreciable amounts omega-3 fatty acids that are longer than 14 carbons, they are obtained primarily from dietary sources

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(i.e., they are “essential” fatty acids). The parent omega-3 fatty acid, α -linolenic acid (ALA), is derived mostly from vegetable seed oils (Figure 1) (10). ALA is converted in the endoplasmic reticulum *via* desaturase and elongase enzymes to the longer chain omega-3 fatty acid eicosapentanoic acid (EPA; Figure 1). Elongation and desaturation of EPA to (small) quantities of docosahexanoic acid (DHA) subsequently occurs in peroxisomes *via* a number of complex steps that are known as the Sprecher pathway (11). The two most bioactive and extensively studied omega-3 fatty acids are EPA and DHA (12). However, enzymatic conversion of ALA to longer chain fatty acids is limited (11), so individuals are likely to rely on dietary consumption to maintain optimal EPA and DHA levels. Cold-water fish is the primary dietary source of EPA and DHA. A comprehensive list of fish and their omega-3 content is included in the survey by Kris-Etherton *et al.* (13). Although detailed data on omega-3 content is very difficult to obtain in part because of regional differences and changes in the composition of animal feed, a consensus exists that meat, poultry, eggs, and grains contain much smaller amounts of omega-3 fatty acids compared with fish (10). Retroconversion of DHA to EPA may also provide very limited quantities of EPA (14).

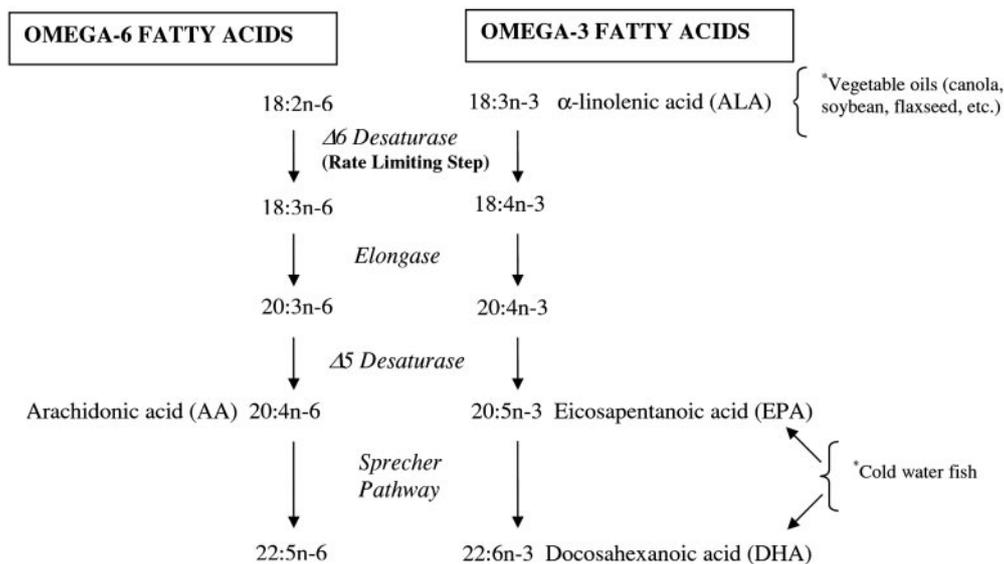
EPA and DHA levels can be modified to a certain extent by factors other than dietary intake. Conversion of ALA to EPA and DHA is greater in young women than men (15). Age also can affect omega-3 levels, perhaps through alterations in desaturase or elongase activity (16). At least in part because of competition among parent omega-3 and omega-6 fatty acids for $\Delta 6$ desaturase (Figure 1), the omega-6:omega-3 ratio can affect conversion of ALA (11). Whether chronic diseases such as diabetes independently alter omega-3 metabolism and levels is controversial (17–20). The possibility that race, ethanol use, and

body size affect fatty acid synthesis has also been raised (17,21,22).

Dietary Reference Intake Adequate Intake recommendations (i.e., highest median US adult intake that prevents essential fatty acid deficiency in the general population) for ALA are defined as 1.6 and 1.1 g/d for men and women, respectively (23). However, there is no defined normative range for blood and tissue omega-3 fatty acid levels or specific US guidelines for EPA and DHA intake, although they are counted toward contributing up to 10% of total omega-3 and, hence, daily ALA requirements (i.e., approximately 0.1 to 0.2 g/d). In contrast, a number of industrialized nations as well as the World Health Organization now recommend consumption of 0.3 to 0.5 g/d EPA + DHA for their general populace (13). This goal is unlikely to be reached by a large proportion of healthy Americans given current dietary consumption patterns (23). Recently, the American Heart Association established evidence-based recommendations for omega-3 fatty acid intake (13). Patients without documented coronary heart disease were advised to eat fish at least twice a week in addition to oils and foods that are rich in ALA, whereas individuals with documented heart disease were encouraged to consume approximately 1 g/d EPA + DHA, preferably from oily fish or supplements. Current US recommendations support an omega-6:omega-3 dietary ratio of at least 5:1 (23).

Omega-3 Fatty Acids: Biologic and Clinical Effects

Omega-3 fatty acids have been investigated for their salutary clinical actions in a number of disease processes that are salient to dialysis patients. Although an extensive review of the liter-



* denotes primary dietary source

Figure 1. Elongation of omega-3 and omega-6 fatty acids.

ature in the non-kidney disease population is beyond the scope of this article, the following general description of the diversity of potential benefits of omega-3 fatty acids is provided as background before presenting the systematic review of the literature in the dialysis population.

Inflammatory States

The omega-6 fatty acid arachidonic acid (AA) is converted intracellularly *via* cyclooxygenase, lipoxygenase, or cytochrome P450 AA monooxygenase to a host of bioactive eicosanoid products, among them prostaglandins, leukotrienes, thromboxanes, lipoxins, epoxyeicosatrienoates, and hydroxyeicosatetraenoates. A number of these AA-derived eicosanoids promote prothrombotic, proinflammatory, or proarteriosclerotic effects, including platelet aggregation, vasoconstriction, chemotaxis, increased vascular permeability, and cytokine release (Figure 2) (24,25). By competing with AA both for incorporation into the lipid pool (in particular, cell membrane phospholipids) and therefore reducing the supply of AA, as well as for the enzymes involved in eicosanoid synthesis, EPA shunts production toward eicosanoids with attenuated or anti-inflammatory and antiarteriosclerotic effects (Figure 2) (25). These include the downregulation of proinflammatory cytokines (26–28) and cell surface molecules involved in cell adhesion and activation (24,29). The mechanism may involve molecules such as resolvin E1, a newly discovered lipid byproduct of EPA that suppresses activation of NF- κ B (30). The effects of omega-3 fatty acids have been demonstrated to have clinical benefits for such diverse inflammation-mediated diseases as rheumatoid arthritis (3),

inflammatory bowel disease (31), and certain skin disorders (32) and nephropathies (33).

Atherosclerosis

Inflammation is believed to play a critical role in the evolution of atherosclerosis (34). By downregulating proinflammatory eicosanoids, omega-3 fatty acids may reduce the risk for atherosclerotic progression (35). Dwyer *et al.* (25) found that certain genotypes of 5-lipoxygenase, which produces leukotrienes (some of which are proinflammatory in nature), were associated with increased atherosclerosis in 500 healthy individuals as measured by carotid intima-media thickness. It is interesting that dietary omega-6 fatty acids seemed to promote, whereas omega-3 consumption inhibited, this atherosclerotic process. A recent meta-analysis of randomized, controlled fish oil trials also supports the premise that omega-3 fatty acids have cardioprotective properties in individuals with established coronary disease (4).

Dysrhythmias

Integration of EPA and DHA into cell membranes modulates membrane ion channel (*e.g.*, Na⁺, L-Ca²⁺) function, which may alter membrane electrical activity (5). In fact, EPA and DHA have been demonstrated in cell culture, animal models, and human studies to increase myocardocyte membrane electrical stability and thereby prevent malignant dysrhythmias, as reviewed by Leaf *et al.* (5). The largest such clinical trial was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione study, which included >11,000 survivors of myocardial infarctions (36). Study patients were randomly assigned to daily fish oil supplementation (approximately 0.9 g of EPA + DHA), vitamin E, fish oil + vitamin E, or no therapy. GISSI reported striking reductions (21 to 45%) in all-cause mortality, cardiovascular death, sudden death, and fatal myocardial infarctions in the fish oil arm. This occurred despite that patients were treated with standard-of-care therapy (*e.g.*, aspirin, statins) and had moderate fish consumption at baseline. Findings of very early reductions in total mortality and sudden death lend further support to the argument that fish oil has antiarrhythmic effects (37). However, a limitation to this study was its open-label design.

Dyslipidemia

Because cell membrane fatty acids play an important role in signal transduction, omega-3 fatty acids are capable of modifying gene expression. It is believed that the dramatic lipid-altering effects of omega-3 fatty acids are mediated *via* this mechanism (38). Specifically, omega-3 fatty acids modulate the function of peroxisome proliferator-activated receptors and sterol regulatory binding proteins, both of which are involved in lipid homeostasis (39,40). This topic was reviewed in detail recently (38). Supraphysiologic omega-3 doses (>3 g/d) in humans can reduce triglyceride levels by 25 to 30% and increase LDL and HDL levels by 5 to 10% and 1 to 3%, respectively (6). Fish-based fatty acids (EPA and DHA) seem to have greater lipid-altering effects than plant-based fatty acids (ALA) (6).

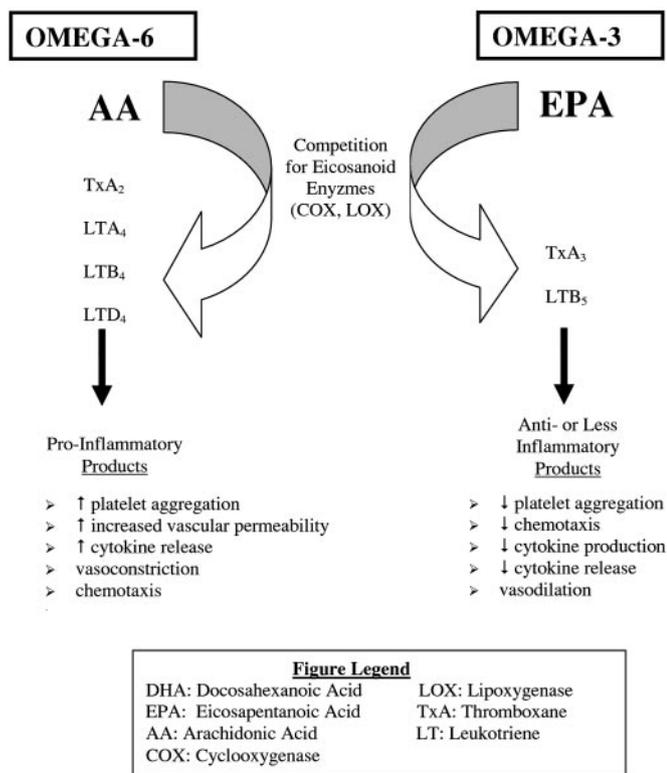


Figure 2. Synthesis of pro- and anti-inflammatory eicosanoids.

Table 1. Omega-3 supplementation studies in dialysis patients sorted by design and year^a

Study	n	RCT	Study intervention			Outcomes			
			Dialysis Modality	Treatment (g/d)	Duration (Weeks)	Variable	Change	P	
Diskin <i>et al.</i> (76), 1990, USA	7	Yes	HD	EPA 3	24	Dialysis graft survival, blood electrolytes, total cholesterol, albumin, liver enzymes, blood viscosity, bleeding time, PT, PTT, white blood cells, hemoglobin	No change	—	
Donnelly <i>et al.</i> (70), 1992, Canada	13	Yes	PD/HD	Fish oil 3.6	4	Omega-3 platelet membrane fatty acids	Increase	<0.05	
De Fijter <i>et al.</i> (75), 1995, The Netherlands	16	Yes	NR	Fish oil 3	20	PT, PTT, bleeding time, platelets, BP, hematocrit, white blood cells, triglycerides, total and HDL cholesterol	No change	—	
Peck <i>et al.</i> (48), 1996, USA	25	Yes ^b	HD	Fish oil 6	8	Omega-3 plasma phospholipid fatty acids	Increase	<0.05	
Christensen <i>et al.</i> (84), 1998, Denmark	17	Yes	HD/PD	Fish oil 5.2	12	BP, plasma viscosity, fibrinogen	No change	—	
Ando <i>et al.</i> (72), 1999, Japan	38	Yes	HD/PD	EPA, 1.8	12	Plasma omega-3 fatty acids	Increase	<0.05	
Lossel <i>et al.</i> (81), 1999, Denmark	16	Yes	HD	Fish oil 5.2	12	Plasma prostaglandin E ₂	Increase	<0.10	
Khajehdehi (71), 2000, Iran	60	Yes	HD	Fish oil 1.5	8	Pruritus severity and distribution	Decrease	<0.10	
Schmitz <i>et al.</i> (73), 2002, USA	24	Yes	HD	Fish oil 3.2	<52	Omega-3 granulocyte fatty acids	Increase	<0.05	
Begum <i>et al.</i> (82), 2004, USA	22	Yes ^b	HD	Fish oil 4.4	16	Electrocardiogram RR interval	7%	<0.05	
Rylance <i>et al.</i> (52), 1984, England	9	No	HD	Fish oil 3.6	8	SD of all normal RR intervals	No change	—	
Hamazaki <i>et al.</i> (54), 1984, Japan	12	No	HD	Fish oil 2.6	13	Plasma EPA levels	220%	<0.05	
Rylance <i>et al.</i> (53), 1986, England	16	No	HD	Fish oil 3.6	8	Remnant plasma lipoproteins	–52%	<0.01	
Van Acker <i>et al.</i> (55), 1987, The Netherlands	9	No	PD	Fish oil 3	8	Oxidized LDL cholesterol	–38%	<0.01	
						Total cholesterol	–16%	<0.01	
						Triglycerides	–42%	<0.01	
						HDL cholesterol, platelets	No change	—	
						Neutrophil-derived leukotriene B ₄	–34%	<0.001	
						Neutrophil-derived leukotriene B ₅ (versus placebo group)	>500%	<0.001	
						HDL cholesterol	139%	<0.001	
						Total and LDL cholesterol, triglycerides	No change	—	
						Omega-3 platelet membrane fatty acids	Decrease	<0.05	
						Triglycerides	–113%	0.07	
						BP	Decrease	<0.05	
						Dialysis graft patency period	436%	<0.03	
						LDL cholesterol, lipoprotein (a)	No change	—	
						Red blood cell DHA content	391%	<0.05	
						Neutrophil-derived leukotriene B ₄	Decrease	NR	
						Red blood cell EPA content, pruritus symptoms	No change	—	
						Triglycerides	–50.6%	<0.005	
						HDL cholesterol	25%	<0.005	
						HDL ₂ cholesterol	51.5%	<0.02	
						Platelet aggregation rate (collagen)	Decrease	<0.01	
						Platelet aggregation maximum (collagen)	Decrease	<0.01	
						Platelet aggregation rate (ADP)	Decrease	<0.02	
						Platelet aggregation maximum (ADP)	Decrease	<0.02	
						Total cholesterol, HDL ₃ cholesterol	No change	—	
						Omega-3 plasma fatty acids	Increase	<0.001	
						Total cholesterol	Decrease	<0.025	
						Triglycerides	Decrease	<0.001	
						Serum phospholipids	Decrease	<0.005	
						Diastolic BP	–9%	<0.05	
						Platelets	–19%	<0.005	
						HDL cholesterol, serum free fatty acids, blood viscosity	No change	—	
						Triglycerides	–35%	<0.001	
						HDL cholesterol	10%	<0.05	
						HDL ₂ cholesterol	36%	<0.02	
						Platelet aggregation rate (collagen)	Decrease	<0.001	
						Platelet aggregation maximum (collagen)	Decrease	<0.001	
						Platelet aggregation rate (ADP)	Decrease	<0.005	
						Platelet aggregation maximum (ADP)	Decrease	<0.01	
						Activated whole-blood clotting time	9%	<0.02	
						Sitting BP	Decrease	<0.05	
						Total cholesterol, HDL ₃ cholesterol, hemoglobin, PT, factor VIII related antigen, platelet count, β thromboglobulin	No change	—	
						Omega-3 plasma fatty acid phospholipids	Increase	<0.01	
						Triglycerides	–30%	<0.05	
						HDL ₂ cholesterol	–20%	<0.05	
						Erythrocyte viscosity	Decrease	<0.05	
						Mean corpuscular volume	–4%	<0.05	
						Total, VLDL, LDL, HDL ₃ cholesterol, glucose, insulin, C peptide, total protein, total free fatty acids, hemoglobin, platelets, BP	No change	—	

Table 1. Continued

Study	n	RCT	Study intervention			Outcomes		
			Dialysis Modality	Treatment (g/d)	Duration (Weeks)	Variable	Change	P
Lempert <i>et al.</i> (56), 1988, USA	11	No	PD	Fish oil 7.6	4	Triglycerides	–29%	<0.01
						HDL cholesterol	–9%	<0.05
						LDL cholesterol	21%	<0.05
						Total cholesterol, albumin, platelets, bleeding time, hematocrit, platelet aggregation, BP	No change	—
Rustemeijer <i>et al.</i> (57), 1988, The Netherlands	9	No	HD	Fish oil 3	8	Omega-3 plasma fatty acid phospholipids	Increase	<0.01
						Total cholesterol	24%	<0.05
						Triglycerides	–14%	<0.05
						VLDL cholesterol	–24%	<0.05
						LDL cholesterol	29%	<0.05
						Total phospholipids	9%	<0.05
						Platelets	–25%	<0.005
						HDL cholesterol, HDL ₂ and HDL ₃ cholesterol, total plasma free fatty acids, total protein and albumin, BP	No change	—
Azar <i>et al.</i> (58), 1989, France	13	No	HD	Fish oil 1.7	4	Triglycerides	–39%	<0.01
						Apolipoprotein B	–17%	<0.01
						BP, hemoglobin, platelets, PT, total cholesterol, apolipoprotein A1	No change	—
Rolf <i>et al.</i> (59), 1990, Germany	10	No	HD	Fish oil 0.4	28	Total cholesterol	–36%	NR
						Triglycerides	–48%	NR
						HDL cholesterol	46%	NR
						LDL cholesterol	–14%	NR
						Serum magnesium	–10%	<0.001
						Serum phosphate	–24%	<0.005
						BP	Decrease	<0.001
Goren <i>et al.</i> (60), 1991, Israel	16	No	HD/PD	Fish oil 3–8	8	Triglycerides	–28%	<0.01
						Total/HDL cholesterol	–12%	<0.05
						Platelets, BP, total and LDL cholesterol, apolipoprotein A1/B	No change	—
Hombrouckx <i>et al.</i> (61), 1992, Belgium	19	No	HD	Fish oil 1.7–2.55	12	Total and HDL cholesterol, triglycerides, total lipids, phospholipids, leukopenia after start of dialysis, reusability of dialyzer membranes, insulin, fibrinogen, bleeding time, BP	No change	—
Fracasso <i>et al.</i> (62), 1992, Italy	6	No	PD	Fish oil 3–4	4	Triglycerides	–73%	<0.001
						Peritoneal solute transport	Increase	<0.05
						Total and HDL cholesterol, apolipoprotein A1 and B	No change	—
Nordkild <i>et al.</i> (77), 1993, Denmark	8	No	HD	Fish oil/anti-oxidants 1.7	16	Erythropoietin dose	–28%	<0.008
						Hemoglobin, reticulocyte count, mean corpuscular volume	No change	—
Dionisio <i>et al.</i> (63), 1994, Italy	14	No	NR	Fish oil 3.15	8	Triglycerides	–47%	<0.001
						HDL cholesterol	39%	<0.003
						LDL cholesterol	–15%	<0.01
						VLDL cholesterol	–28%	<0.01
						Apolipoprotein A1	29%	<0.001
						Apolipoprotein B	–29%	<0.001
						Fibrinogen	–35%	<0.001
						Total cholesterol	No change	—
Panzetta <i>et al.</i> (67), 1995, Italy	14	No	HD	Fish oil 3	4	Total cholesterol	–12%	<0.01
						VLDL cholesterol	–21%	<0.01
						LDL cholesterol	–15%	<0.01
						Triglycerides	–17%	<0.01
						VLDL triglycerides	–28%	<0.01
						LDL triglycerides	–26%	<0.01
						HDL triglycerides	–22%	<0.01
						Susceptibility of LDL to oxidation	Increase	NR
						HDL cholesterol	No change	—
Van Acker <i>et al.</i> (55) and Liani <i>et al.</i> (80), 1995, Italy	10	No	NR	Fish oil 2	4	CD8 lymphocytes	–19%	<0.001
						CD4/CD8 ratio	24%	<0.001
						CD22 lymphocytes	19%	<0.05
						CD3 and CD4 lymphocytes, IgG, IgA, IgM	No change	—
Holdt <i>et al.</i> (69), 1995, Germany	7	No	PD	Fish oil 67.5 (?)	12	IL-6	–11%	NR
						Soluble IL-2 receptor	–50%	NR
						Homocysteine	18%	NR
						Total cholesterol, homocysteine, triglycerides, HDL and LDL cholesterol, fibrinogen, plasma viscosity, erythrocyte deformability, thrombocyte and erythrocyte aggregation, dialysate solute clearance	No change	—

Table 1. Continued

Study	n	RCT	Study intervention			Outcomes			
			Dialysis Modality	Treatment (g/d)	Duration (Weeks)	Variable	Change	P	
Bonanome <i>et al.</i> (68), 1996, Italy	12	No	HD	Fish oil 2.5	16	LDL cholesterol omega-3 fatty acids	Increase	<0.01	
						Total cholesterol	9%	<0.01	
						Triglycerides	–30%	<0.001	
						LDL cholesterol	29%	<0.001	
						VLDL cholesterol	–36%	<0.001	
Vitamin E, HDL cholesterol, theoretical susceptibility of LDL cholesterol to oxidation	No change	—							
Persichetti <i>et al.</i> (64), 1996, Italy	18	No	HD	Fish oil 3	24	Total cholesterol	Reduction	NR	
						Triglycerides	–55%	NR	
						LDL cholesterol	–19%	NR	
						Fibrinogen	–35%	NR	
						HDL cholesterol	No change	—	
Iorio <i>et al.</i> (65), 1997, Italy	26	No	HD	Fish oil 3.4	12	Triglycerides	Decrease	NR	
						Total, HDL, and LDL cholesterol (Data exclude 9 nonresponders)	No change	—	
Yorioka <i>et al.</i> (66), 2000, Japan	18	No	PD	Fish oil 1.8	8	Triglycerides	–31%	<0.01	
						Apolipoprotein A2	–12%	<0.05	
						Apolipoprotein C3	–25%	<0.05	
						Apolipoprotein E	–26%	<0.01	
						Protein C	–32%	<0.01	
						tPA/PAI	–16%	<0.05	
						Factor XIII	–25%	<0.01	
						α_2 -plasmin inhibitor	–21%	<0.01	
						D-dimer	–33%	<0.05	
						Total and HDL cholesterol, apolipoproteins A1, B, C2, lipoprotein (a), factors IX, VII, X, α_2 -plasmin inhibitor/plasmin complex, antithrombin III, thrombin-antithrombin complex II, protein S, fibrinogen, thrombomodulin, plasminogen	No change	—	
						Triglycerides	–13%	0.07	
						VLDL cholesterol	–18%	<0.05	
						Plasma homocysteine	23%	<0.01	
Arterial pH	–2%	<0.005							
Total, HDL, and LDL cholesterol, complement factors C3 and C4, C-reactive protein, BP, heart rate variability, pruritus and taste scores, dialysis access function, peripheral oxygen saturation	No change	—							
Fiedler <i>et al.</i> (78), 2005, Germany	11	No	HD	Fish oil 1.2	12	Triglycerides	–13%	0.07	
						VLDL cholesterol	–18%	<0.05	
						Plasma homocysteine	23%	<0.01	
						Arterial pH	–2%	<0.005	
Total, HDL, and LDL cholesterol, complement factors C3 and C4, C-reactive protein, BP, heart rate variability, pruritus and taste scores, dialysis access function, peripheral oxygen saturation	No change	—							

^aRCT, randomized, controlled trial; HD, hemodialysis; PD, peritoneal dialysis; EPA, eicosapentanoic acid; DHA, docosahexanoic acid; PT, prothrombin time; PTT, partial thromboplastin time; NR, not reported.

^bLacks placebo-controlled group.

Hypertension

At supraphysiologic doses (>3 g/d), EPA and DHA have the potential to reduce BP significantly in untreated hypertensive individuals (7), possibly by modulating the synthesis of the eicosanoids hydroxyeicosatetraenoates or epoxyeicosatrienoates (41).

Adverse Effects

Data on adverse effects of omega-3 supplementation are restricted primarily to those of fish oil. The risk for increased bleeding times has been seen, primarily with >3 g/d fish oil, although findings are not unequivocal. The clinical implications of this are not clear. Increases in serum glucose and LDL levels have also been seen with large fish oil doses (*e.g.*, >4.5 g/d). Gastrointestinal complaints (*e.g.*, fishy aftertaste, nausea, stomach upset) have been commonly reported (36). Finally, methylmercury and organochlorine concentrations can vary widely in fish oil supplements, depending on the quality of the refining process (42). A more detailed discussion of these ad-

verse effects can be found in the Food and Drug Administration ruling on menhaden oil (43).

Omega-3 Status in Dialysis Patients

There are a number of reasons to suspect that omega-3, particularly EPA and DHA, blood and tissue status may be inadequate in the dialysis population. First, hemodialysis patients may find foodstuffs that are the major sources of EPA and DHA (*i.e.*, fish and meat) to be less palatable, perhaps because of uremia-associated alterations in taste (44). Second, fish consumption, the primary dietary source of EPA and DHA, may be limited by social dietary habits and financial constraints present in the US dialysis population. Third, formal renal dietary recommendations that specifically encourage fish consumption do not exist. Fourth, hemodialysis is believed to upregulate oxidative mechanisms, which could potentially lead to increased omega-3 peroxidation (45). Peroxidation ultimately leads to breakdown of fatty acyl structure and loss of biologic function. Finally, consumption of the omega-3 parent fatty acid ALA

may potentially be reduced as a result of kidney disease–related potassium dietary restriction.

However, only very limited data exist describing fatty acid levels in dialysis patients. Three studies noted low plasma levels of parent omega-3 and/or omega-6 fatty acids (46,47), AA (46–48), and EPA (48,49) compared with matched controls. A fourth found low red blood cell membrane EPA levels (49). Interpretation of these findings, however, is hindered for the following reasons: Very small study sample sizes (n ranging between 9 and 25); missing data on EPA, DHA, and other fatty acid levels or important fatty acid ratios (*e.g.*, omega-6:omega-3); heterogeneity in study measurements (*i.e.*, plasma *versus* red blood cell levels); differences in subject ethnicity and origin (one European, one African, two North American) that could affect omega-3 dietary intake; and heterogeneity in study inclusion criteria. Clearly, more work needs to be done in defining omega-3 status in the dialysis population.

Effects of Omega-3 Supplementation in Dialysis Patients

Omega-3 supplementation studies have examined a variety of clinical outcomes that are relevant to dialysis patients, as noted in Table 1. The majority of trials were small and uncontrolled, and all administered omega-3 in the form of fish oil. Of note, compliance was not confirmed routinely by tissue omega-3 measurements.

Dyslipidemia

Omega-3 has an established lipid-altering effect (50), and lipid derangements, particularly hypertriglyceridemia and reduced HDL levels, are commonly exhibited by dialysis patients (51). Although >20 studies (52–73) have measured the effects of fish oil supplementation on lipid status in the dialysis population, only four were randomized and controlled in nature. Donnelly *et al.* (70) found that 3.6 g/d fish oil in a mixed dialysis population reduced triglyceride levels compared with placebo (2.0 ± 0.4 *versus* 3.5 ± 0.3 mmol/L) but only when one patient (of 13) with severe hypertriglyceridemia was excluded from the analysis. Three larger studies reported that smaller daily fish oil doses (1.5 to 3.2 g) significantly reduced triglyceride levels compared with placebo (71–73). One of these trials also noted a reduction in remnant lipoproteins by nearly 50% at 12 wk (72). Of note, compliance was confirmed in three of the four trials.

Nearly all of the remaining uncontrolled studies (52–69) found that fish oil supplementation dramatically reduced triglycerides but had mixed effects on other lipoproteins. Most used supraphysiologic omega-3 doses (≥ 2 to 3 g/d) but differed widely in size ($n = 6$ to 26), patient population (peritoneal *versus* hemodialysis), and treatment length (4 to 28 wk). Although fish oil seems to improve the lipid profile at high doses, its effects at more modest doses are unknown.

Hematologic

Because of the putative benefits of omega-3 fatty acids on red blood cell deformability and aggregation (8,74), a number of studies have investigated these effects in dialysis patients, al-

though only two were randomized and controlled (70,75). Overall, there are no clear effects of fish oil–derived omega-3 fatty acids on platelet aggregation, blood viscosity, red blood cell survival, and bleeding times, even at high doses (1.7 to 7.6 g/d) (52–56,58,69,70,75–77). Four of eight studies found a reduction in platelet counts (54,56,57,66), although only one dropped below the normative range (54). No effect on the prothrombin or partial thromboplastin times was documented (53,70,76). Although reductions in fibrinogen levels were noted in two uncontrolled cohorts (63,64), this finding was not replicated under controlled conditions (75). Finally, Yorioka *et al.* (66) described reductions in a host of coagulation factors, including protein C, factor XIII, α_2 -plasmin inhibitor, and D-dimers, after treating 18 patients with 1.8 g of EPA for 8 wk. The clinical significance of these findings is not yet known.

Blood Pressure

BP reduction is another potential benefit of omega-3 supplementation (7). Of the 12 studies performed in dialysis patients that measured this end point (54–59,61,70,71,73,75,78), only four used a randomized, controlled design (70,71,73,75). Three of the 12 studies reported that fish oil therapy significantly reduced diastolic (7 to 15 mmHg) and/or systolic BP (16 to 30 mmHg) (54,59,73). The only controlled study with positive findings noted a dramatic reduction in systolic and diastolic pressures, although this study was not designed with BP as a primary outcome (73). Thus, the antihypertensive effect of omega-3 supplementation in dialysis remains to be proved.

Dialysis Access

Because of its antithrombotic, anti-aggregatory, and antiproliferative actions (79), fish oil may be effective in improving dialysis shunt patency rates. Two trials, both randomized and controlled, have examined this question. Diskin *et al.* (76) reported that four patients who consumed 3 g/d fish oil for 6 mo had no outflow stenosis by duplex ultrasonography compared with two of three who were on placebo and did have outflow stenosis. However, there was no overall difference in graft survival. Schmitz *et al.* (73) randomly assigned 24 patients who underwent new arteriovenous graft placements to 3.2 g/d fish oil *versus* placebo. Patients were followed up to 1 yr or until graft thrombosis developed. The overall patency rate in the fish oil group and the placebo group was 76 *versus* 15%, respectively. A trend toward an increase in venous outflow pressures was seen only in the placebo group. Compliance was confirmed by platelet membrane fatty acid measurements. Thus, fish oil holds promise as an effective prophylaxis against shunt thrombosis.

Immune Response and Inflammation

Omega-3 fatty acids display immunomodulatory properties *via* a variety of previously reviewed mechanisms. Data in dialysis patients are derived from small, primarily uncontrolled cohorts. Omega-3 supplementation has been shown to alter lymphocyte subpopulations (80) but not levels of the human leukocyte antigen DR (69) or complement components C3 and C4 (78). These studies also report conflicting effects on cytokine

and arteriosclerotic risk factor levels, such as IL-6, soluble IL-2 receptors, C-reactive protein, and homocysteine (69,78). Three randomized studies (one placebo controlled) did find that omega-3 supplementation shunted leukocyte production away from proinflammatory (*e.g.*, leukotriene B₄) to much less or anti-inflammatory eicosanoid products (*e.g.*, leukotriene B₅) (48,81,82). In summary, although the biologic mechanisms underlying fish oil's effects on inflammation and immunity are well understood, the clinical effects, particularly using modest doses, need to be defined more clearly.

Oxidative Stress

Omega-3 fatty acids are highly susceptible to oxidation because of their multiple double bonds. Because the state of ESRD may lead to increased lipid peroxidation (45), which is itself linked to atherosclerosis (83), the possibility exists that omega-3 supplementation in dialysis patients may have potentially adverse cardiovascular effects. However, studies in dialysis patients that have measured the susceptibility of LDL particles to oxidation have not supported this concern (67,68). Although one such study did find that susceptibility was increased, omega-3 fatty acids also seemed to increase the antioxidant capacity of LDL particles. Moreover, Ando *et al.* (72) directly measured in randomized, controlled manner the effects of 12 wk of 1.8 g/d EPA supplementation on plasma oxidized LDL particles. Compliance was confirmed by fatty acid plasma measurements. Levels of oxidized LDL were significantly lower (by 38%) by 12 wk compared with baseline (and unchanged in the placebo group). The authors suggested that EPA may have actually protected LDL against peroxidation or improved the body's ability to scavenge oxidative species. However, they could not rule out the possibility that benefits were obtained from the antioxidant α -tocopherol contained in the EPA capsules. Overall, data on omega-3 fatty acids have not supported concerns that they upregulate oxidative stress, although more work is needed to resolve this issue definitively.

Cardiovascular

The beneficial effects of fish oil-derived omega-3 fatty acids on cardiovascular health and mortality in the general population have been reviewed previously (13). Christensen *et al.* (84) measured the effects on heart rate variability of high-dose omega-3 supplementation in 29 dialysis patients in a 12-wk randomized, placebo-controlled study. Because of a high dropout rate in both groups as a result of nausea, direct comparison of groups could not be performed. The authors found that individuals with higher EPA and DHA levels had greater variability in their electrocardiogram RR intervals over a 24-h monitored period. Another uncontrolled study found no difference in heart rate variability with omega-3 supplementation (78). It is interesting that one prospective cohort trial reported that patients who consumed more fish at the time of dialysis initiation had lower mortality risk over the ensuing 3 yr, although the causes of death were not specified and not all cardiovascular risk factors were accounted for in the analysis (85). In conclusion, the cardioprotective effects of omega-3 fatty acids remain a generally unexplored field.

Uremic Pruritus

Because eicosanoids have been proposed as mediators of dermatitis (32), the effect of omega-3 fatty acids on dialysis-associated uremic pruritus has been a focus of study. Two randomized trials found a trend toward an improvement in pruritus symptoms in individuals who took omega-3 compared with omega-6 and omega-9 supplementation (48,82). Further investigation into this question seems warranted.

Adverse Effects

Although not all dialysis studies reported side effects, omega-3 supplementation generally was well tolerated, especially given the high doses used. However, the great majority of studies were not designed to measure side effects and tolerability over long-term use. Most adverse effects involved gastrointestinal complaints such as nausea, vomiting, diarrhea, dysgeusia, and abdominal discomfort. Serious bleeding complications were isolated to a single patient in one uncontrolled study (76).

Conclusion

Omega-3 fatty acids play an important modulatory role in the immune and inflammatory responses, the progression of arteriosclerosis, vascular reactivity and BP control, cell membrane function, and gene expression. On the basis of laboratory data and preliminary clinical findings, there are reasons to suggest that omega-3 supplementation may offer a host of benefits to dialysis patients. In fact, the 2005 Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines specifically encourage further research on the effects of kidney failure and/or dialysis on omega-3 metabolism and blood/tissue levels, as well as the initiation of clinical trials designed to evaluate the effects of omega-3 supplementation on cardiovascular risk and outcomes (9). Unfortunately, the preponderance of published studies on the effects of such supplementation are characterized by suboptimal study design, small sample sizes, supraphysiologic omega-3 doses that may be difficult to consume for extended periods, little long-term follow-up, and a lack of confirmation of compliance. At present, the data in dialysis patients most strongly support the use of omega-3 supplementation for the treatment of hypertriglyceridemia and to improve dialysis access patency rates. However, even these positive findings are derived from studies with notable limitations (*e.g.*, small sample sizes, modest follow-up). In addition, the health risk of omega-3 therapy in dialysis patients has yet to be evaluated formally over long periods, although the accumulated experience thus far suggests that it is relatively safe. In summary, although preliminary data suggest that omega-3 supplementation (using approximately 3 g/d) may have useful clinical benefits in dialysis patients, formal recommendations mandating omega-3 supplementation are premature until long-term and adverse effects are better defined.

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