The Long-Term Outcome of Patients with IgA Nephropathy Treated with Fish Oil in a Controlled Trial

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Abstract. It was reported previously that dietary fish oil supplementation retarded the progression of renal disease in patients with IgA nephropathy in a multicenter, placebo-controlled, randomized, 2-yr clinical trial. The aim of this study was to determine the long-term influence of fish oil treatment on renal progression in observations on the study cohort of 106 patients extending beyond the 2-yr trial. Renal function was assessed by serial serum creatinine and 24-h urine protein measurements. Vital, end-stage renal disease (ESRD), and BP status and treatment beyond completion of the 2-yr trial were determined. As in the trial, the primary end point was an increase of 50% or more in the serum creatinine, and the secondary end point was ESRD. After a mean follow-up of 6.4 yr, 46 patients—17 in the fish oil group *versus* 29 in the placebo group—reached the primary end point ($P = 0.002$), and 27 patients—eight in the fish oil group *versus* 19 in the placebo group—developed ESRD ($P = 0.009$). At the end of the 2-yr trial, 75 patients (45 fish oil, 30 placebo) remained at risk for the primary end point. This is also when the double-blind part of the trial ended, allowing physicians to stop supplements, switch original placebo-assigned patients to fish oil, and continue fish oil in original fish oil-assigned patients. A significantly greater number of nonsupplemented placebo patients developed the primary end point ($P = 0.02$) and ESRD ($P = 0.003$) compared with long-term supplemented fish oil patients. Conversely, more fish oil-supplemented patients had stable renal function than nonsupplemented patients ($P = 0.02$). By intention, BP control, primarily treated with angiotensin-converting enzyme inhibition, was equal in the fish oil and placebo groups. Proteinuria was modestly reduced in both groups. It is concluded that early and prolonged treatment with fish oil slows renal progression for high-risk patients with IgA nephropathy.

In 1994, we reported that dietary fish oil supplementation retarded the progression of renal disease in patients with idiopathic IgA nephropathy in a multicenter, placebo-controlled, randomized, 2-yr clinical trial (1). Only 6% of patients had an increase in their serum creatinine concentrations by 50% or more during treatment with a daily dose of 12 g of fish oil, providing 1.9 g of eicosapentanoic acid (EPA) and 1.4 g of docosahexanoic acid (DHA), the two major omega-3 polyunsaturated fatty acids in fish oil, compared to 33% of patients in the olive oil placebo group. Also, the cumulative percentage of patients who developed end-stage renal disease (ESRD) or died was 40% in the placebo group after 4 yr compared to 10% in the fish oil group.

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[a] See Appendix for participating investigators and affiliated organizations.

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The omega-3 fatty acids compete with arachidonic acid to produce trienoic eicosanoids which, in turn, may slow renal disease progression by reducing glomerular and interstitial inflammation, mesangial cell contractility, platelet aggregation, and vasoconstriction in response to renal injury (2).

In this report, we examine the long-term influence of fish oil treatment on renal progression in observations on the study cohort extending beyond the 2-yr trial.

Materials and Methods

Patients and Study Design

All 106 patients who entered the clinical trial were considered for this observational extension of study in which renal function was assessed by serial serum creatinine concentrations and 24-h urine protein measurements. Vital, ESRD, and BP status were determined to date. The change from the randomized clinical trial to the open-label observational study took place when all patients who had not already concluded study reached the proscribed 2-yr follow-up period of the clinical trial. This time period ranged from June 1990 to December 1993 as each patient completed his or her 2 yr. We also documented the number of patients in the original fish oil group who continued supplements, the number of originally assigned placebo-treated patients who were switched to fish oil, the supplements used, the dose, and the duration of fish oil treatment after the 2-yr trial. In patients who completed the double-blind 2-yr trial, investigators, who were

also personal physicians to the patients enrolled in this trial, were free to continue fish oil in those assigned to the fish oil group and to switch to fish oil those assigned to the placebo group.

Three fish oil supplements were used by patients after completing the 2-yr trial: (*1*) MaxEPA (Seven Seas Health Care, Hull, United Kingdom), given in a dosage of six 1-g soft gelatin capsules twice daily providing 1.9 g of EPA and 1.4 g of DHA; (*2*) ethyl esters (obtained from the Fish Oil Test Materials Program, sponsored by National Institutes of Health and the National Oceanic and Atmospheric Administration based at the Southeast Fisheries Science Center, National Marine Fisheries Service, Charleston, SC), given in a daily dosage of five 1-g soft gelatin capsules providing 1.8 g of EPA and 1.4 g of DHA; and (*3*) Omacor™ (Pronova Biocare, Lysaker, Norway), a highly concentrated form of omega-3 fatty acids, given in a daily dosage of four or eight 1-g soft gelatin capsules providing 1.9 to 3.8 g of EPA and 1.4 to 2.8 g of DHA to patients with progressive IgA nephropathy who entered an ongoing, open-label, randomized comparative dose study (J. V. Donadio Jr, T. S. Larson, E. J. Bergstralh, K. P. Offord, D. C. Spencer, J. P. Grande, for the Mayo Nephrology Collaborative Group. A prospective comparative study of two doses of Omacor™ in the treatment of patients with IgA nephropathy, study in progress).

The majority of patients had their follow-up serum creatinine concentrations and 24-h urine protein determinations performed at the same central laboratory used to analyze these two parameters during the trial. Each collaborating physician caring for a patient in the trial submitted this information on case report forms that were analyzed at the Coordinating Center at the Mayo Clinic (Rochester, MN).

Statistical Analyses

The cumulative percentage of patients who progressed to the primary end point of the study, defined as an increase of 50% or more in the serum creatinine above baseline to last follow-up, was calculated using the Kaplan–Meier method (3). During the 2-yr treatment period of the trial, 12 patients (six fish oil- and six placebo-assigned) were noncompliant. In these subjects, information concerning the primary end point was censored without the event having occurred to the time of noncompliance. During the 2-yr trial and the following observational phase of study, the vital and ESRD status of all noncompliant patients was determined retaining them in their original treatment group on the intent-to-treat principle. The cumulative percentage of all patients with the secondary end point of ESRD was also calculated by the Kaplan–Meier method (3). Comparisons of both the primary and secondary end points between fish oil and placebo groups were made using the log-rank test (4). Linear regression analysis was used to estimate the annual rates of change in urine protein excretion for each patient.

Results

In extended observations of the 106 patients enrolled in the study, the mean (median) follow-up was 6.4 (6.8) yr with 65, 31, and 13 patients at risk (alive without ESRD) at 5, 7, and 8 yr, respectively. Patients in the placebo group had a significantly greater frequency of adverse renal outcomes than those in the fish oil group (Table 1). Forty-six patients (17 in the fish oil group and 29 in the placebo group) reached the primary end point with respective 5-yr Kaplan–Meier event-free survival estimates of 79 and 49% ($P = 0.002$) (Figure 1). Twenty-seven patients (eight in the fish oil group and 19 in the placebo group) developed ESRD with respective 8-yr event-free survival estimates of 85 and 56% ($P = 0.009$) (Figure 2). Nineteen of 27 patients (70%) who developed ESRD were men, and eight of 27 patients (30%) were women, which is similar to the gender distribution of patients who were enrolled in the trial, *i.e.*, 79 men (75%) and 27 women (25%).

Table 1. Vital and renal outcome status of 106 patients with IgA nephropathy who entered a placebo-controlled, randomized clinical trial of fish oil treatment

Outcome	Fish Oil Group ($n = 55$)	Placebo Group ($n = 51$)	P Value[a]
Primary end point[b]	17	29	0.002
during the 2-yr trial	3	14	
after the 2-yr trial	14	15	
End-stage renal disease[c]	8	19	0.009
during the 2-yr trial	4	4	
after the 2-yr trial	4	15	
Deaths[d]	1	3	

[a] Log-rank test.
[b] Defined as an increase of 50% or more in the serum creatinine above baseline.
[c] Defined as requiring repeated dialysis or renal transplantation.
[d] The fish oil-treated patient had stable renal function and died of metastatic adenocarcinoma of the lung; two placebo-treated patients who died also had end-stage renal disease—one patient died of metastatic oat cell carcinoma of the lung and one patient died of a postrenal transplant lymphoproliferative disorder (B cell lymphoma); one placebo-treated patient had stable renal function and died of acute myocardial infarction 3 yr after study entry.

Forty-five of the 55 patients in the original fish oil group remained at risk for the primary end point at the end of the 2-yr trial, and 44 of them continued taking fish oil beyond 2 yr, 34 on a continuous, daily basis and 10 intermittently (Table 2). One patient in the fish oil group was lost to follow-up after completing 2 yr. Thirty of the 51 patients in the original placebo group were at risk for the primary end point at the end of the 2-yr trial; 17 patients were switched to fish oil, 14 taking supplements on a continuous, daily basis and three intermittently, and 13 patients did not take fish oil after completing the 2-yr trial (Table 2).

Of the 75 patients still at risk for the primary end point after 2 yr, the 13 nonsupplemented placebo patients were not more progressive than the original placebo group (serum creatinine 1.4 ± 0.5 mg/dl [mean ± SD] *versus* 1.5 ± 0.5 mg/dl, respectively [$P = 0.2$, two-sample t test]). And the 17 placebo patients switched to fish oil were not more progressive when they started fish oil from year 2 onward (serum creatinine 1.6 ± 0.5 mg/dl) than the 45 patients in the original fish oil group at baseline (serum creatinine 1.4 ± 0.4 mg/dl) ($P = 0.1$, two-sample t test). A significantly greater number of nonsupplemented patients in the placebo group developed both the primary end point ($P = 0.02$) and ESRD ($P = 0.003$) compared with the long-term supplemented patients in the fish oil group (Table 2).

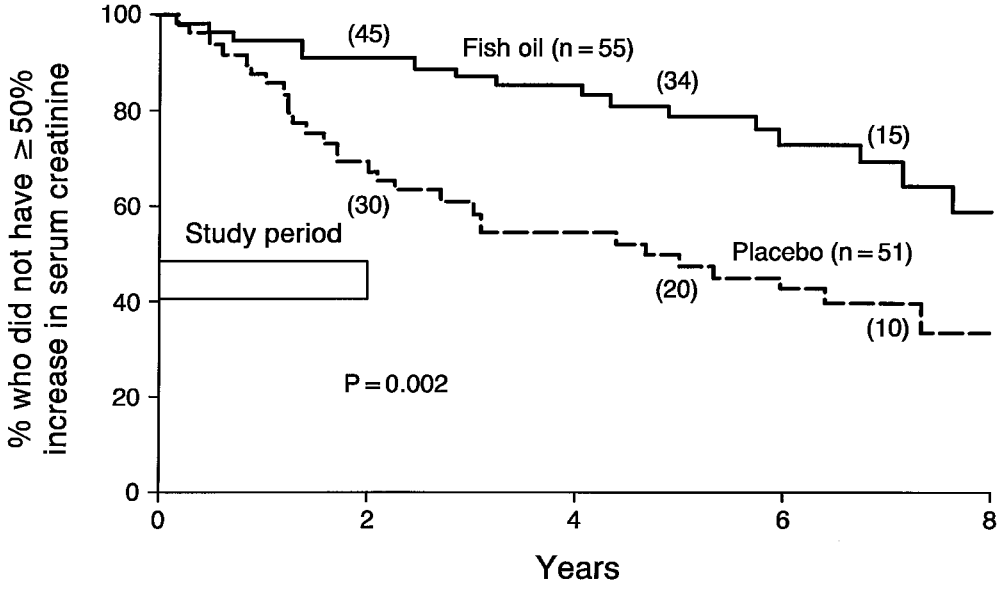

Figure 1. Cumulative percentage of patients with IgA nephropathy treated with fish oil or placebo whose serum creatinine did not increase by 50% or more to last follow-up. Forty-four patients in the fish oil group and 17 patients in the placebo group received fish oil from year 2 onward and were at risk for the primary end point at the end of the 2-yr trial. Thirteen at-risk patients in the placebo group did not take fish oil for the duration of their follow-up (n = number of patients at risk).

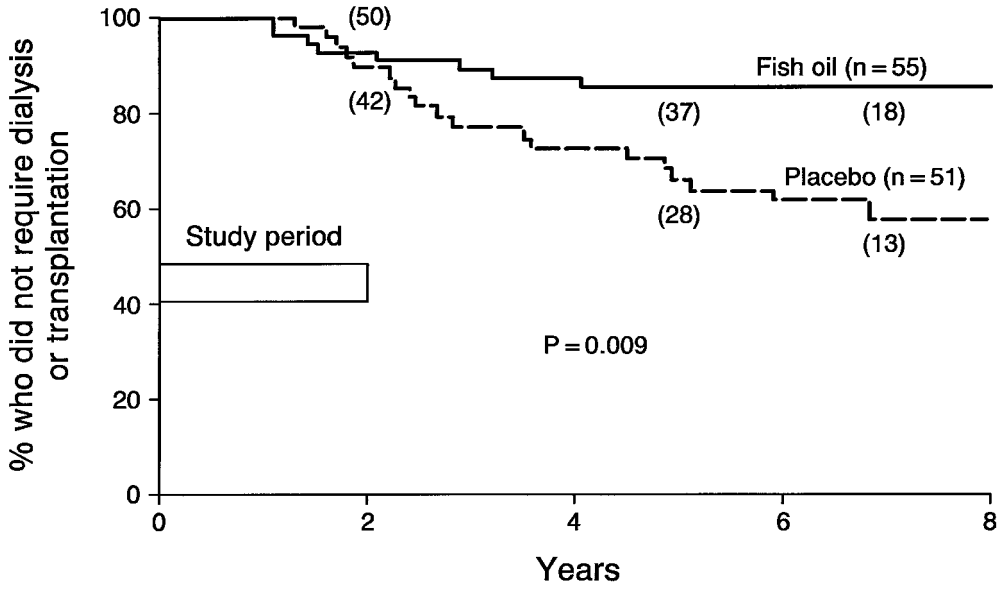

Figure 2. Cumulative percentage of patients with IgA nephropathy treated with fish oil or placebo who did not develop end-stage renal disease to last follow-up (n = number of patients at risk).

In the extended use of fish oil, 40 patients in the original fish oil group and 14 in the original placebo group were supplemented with MaxEPA. Eleven patients (seven fish oil, four placebo) were given Omacor™, either 4 or 8 g daily according to study protocol (J. V. Donadio Jr, T. S. Larson, E. J. Bergstralh, K. P. Offord, D. C. Spencer, J. P. Grande, for the Mayo Nephrology Collaborative Group. A prospective comparative study of two doses of Omacor™ in the treatment of patients with IgA nephropathy, study in progress), and six patients in the fish oil group and one patient in the placebo group received MaxEPA (4) and U.S. Marine ethyl esters (2) before starting Omacor™. Three patients in the fish oil group received ethyl esters followed by MaxEPA. No serious adverse reactions to fish oil were reported.

Baseline (time 0) 24-h urine protein excretion was 2545 ± 1712 mg (mean ± SD) in the fish oil group and 3222 ± 3211 mg in the placebo group (P = 0.5, two-sample t test). The median annual percent changes in proteinuria were −14.6% (−230 mg) in the fish oil group and −6.6% (−100 mg) in the placebo group (P = 0.22, two-tailed P value from rank-sum

Table 2. Renal outcome according to treatment group from year 2 onward in patients who had not progressed to the primary end point during the 2-yr trial

Treatment Group	No. of Patients	Renal Outcome % (*n*)		
		Stable Renal Function	Primary End Point	End-Stage Renal Disease
Fish oil	45[a]	69 (31)[b]	31 (14)[b]	2 (1)[c]
Placebo	30			
switched to fish oil	17	65 (11)	35 (6)	24 (4)
no supplements	13	31 (4)[b]	69 (9)[b]	31 (4)[c]

[a] Forty-four patients continued fish oil after completing the 2-yr clinical trial. One patient was lost to follow-up after 2 yr.
[b] $P = 0.02$, Fisher exact test comparing placebo patients with no supplements after 2 yr with fish oil patients.
[c] $P = 0.003$, Fisher exact test comparing placebo patients with no supplements after 2 yr with fish oil patients.

test), and the reductions were similar between hypertensive and normotensive subjects in both treatment groups (Table 3). In addition, seven of 55 (13%) originally assigned fish oil-treated patients and one of 51 (2%) originally assigned placebo-treated patients ($P = 0.04$, χ^2 test) had a final 24-h urine protein excretion <300 mg. This degree of urine protein reduction is the clinical benchmark for resolution of proteinuria.

An intended goal of the study was to treat all hypertensive patients with the angiotensin-converting enzyme inhibitor (ACEi) enalapril, regardless of the supplements to which they were assigned. Thirty-two fish oil-treated and 29 placebo-treated patients received enalapril in doses ranging from 5 to 40 mg/d during and after the 2-yr trial. Thus, the reduction in urine protein was not greater in the patients treated with doses of enalapril usually used to control hypertension than that observed in normotensive patients. Baseline and final follow-up BP recordings are shown in Figure 3. Goal BP control, achieving a 130/80 mmHg range, was equally maintained in fish oil and placebo groups in both hypertensive and normotensive patients defined at study entry.

Discussion

Long-term dietary fish oil supplementation reduced renal disease progression consistent with the findings in our reported 2-yr clinical trial (1). Both the primary end point, an increase of 50% or more in the serum creatinine, and ESRD were substantially lower in the fish oil group in observations averaging 6.4 yr from randomization to last follow-up. Although the original placebo group did not remain a pure control group after the double-blind part of the trial was concluded, 13 patients did not take fish oil for the entire study period. A significantly greater number of the nonsupplemented patients developed both the primary end point and ESRD than did those in the original fish oil group who continued taking fish oil.

Table 3. Annual changes in 24-h urine protein excretion in fish oil and placebo groups

Group	Annual Change[a] mg (%)	Hypertensive (mg)	Normotensive (mg)	*P* Value[b]
Fish oil	−230 (−14.6)	−278	−219	0.46
Placebo	−100 (−6.6)	−151	−49	0.3

[a] Median.
[b] Two-tailed *P* value from the rank-sum test comparing annual changes in proteinuria in hypertensive and normotensive fish oil and placebo groups.

In three small-sample, randomized clinical trials that also assessed the efficacy of fish oil treatment for patients with IgA nephropathy, one study (1 yr of treatment) demonstrated a beneficial effect on reducing renal progression (5) while two others (6 mo and 2 yr of treatment) did not (6,7). Reasons for these discrepant results are not fully clear but may be related to length of follow-up. IgA nephropathy is most often a slowly progressive disease in which long-term follow-up is needed to demonstrate therapeutic efficacy. As pointed out in a recent meta-analysis of the clinical trials that tested fish oil in IgA nephropathy, 44% of the interstudy variance could be attributed to differences in follow-up times (8). Other differences in the outcomes may relate to BP control (hypertension is a strong risk for progression of renal disease in patients with IgA nephropathy) or stage of disease at the time of study (patients with advanced disease, as evidenced by serum creatinine >3.0 mg/dl, may develop progressive renal failure despite therapy) (9,10).

Criticism has been leveled that the main reason for the results favoring fish oil in our trial is because there was an inordinately high progression rate in the placebo group (11). To address this criticism, at study entry, all patients had a urinary protein excretion rate of 1 g/24 h or more, 58% were hypertensive, and 68% had an elevated serum creatinine, factors that constitute a high-risk profile (12–15). All of these clinical features were equally distributed in the fish oil and placebo groups in our study (1). The progression rate in the placebo group was also similar to that found in high-risk patients reported from Sweden (16) and Canada (17), in which annualized changes in estimated GFR could be compared (18). Furthermore, the decreases in GFR found in the Swedish, Canadian, and our placebo-treated patients were significantly greater than those found in the fish oil group, providing further evidence for the renal function-preserving effects of fish oil (18).

Despite the differences in renal end points favoring the fish oil group, the overall reduction in urine protein was modest and not different between fish oil and placebo groups, or between normotensive and hypertensive patients, the latter having been treated primarily with an ACEi. However, the magnitude of reduction in proteinuria is similar to that achieved in two other studies reporting the effects of ACEi in patients with IgA nephropathy (17,19), the majority of whom had urine protein levels in the subnephrotic range as was the case with our patients.

Optimal therapy for all patients with IgA nephropathy, most often a slowly progressive disease, remains to be established.

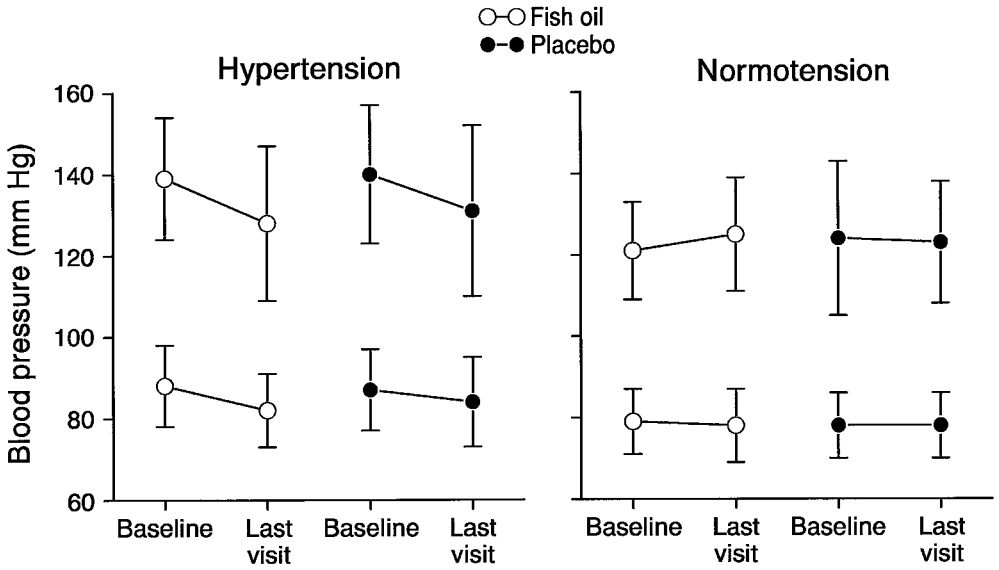

Figure 3. Changes in BP in fish oil and placebo groups comparing BP status at baseline and last follow-up visit. Hypertension was defined at study entry as a systolic pressure of more than 140 mmHg and a diastolic pressure of more than 85 mmHg or in a patient being treated for hypertension. BP recordings are plotted as means ± SD.

Although our studies have shown that fish oil, providing most commonly a daily intake of 1.9 g of EPA and 1.4 g of DHA, slows renal progression, optimal dosing regimens need to be established (J. V. Donadio Jr, T. S. Larson, E. J. Bergstralh, K. P. Offord, D. C. Spencer, J. P. Grande, for the Mayo Nephrology Collaborative Group. A prospective comparative study of two doses of Omacor™ in the treatment of patients with IgA nephropathy, study in progress). Elucidating a mechanistic hypothesis whereby fish oil prevents progression of IgA nephropathy is hampered by the lack of understanding of pathogenetic mechanisms of renal disease. Additional studies are needed to define the role of fish oil in preventing glomerulosclerosis and interstitial fibrosis, the morphologic hallmarks of irreversible renal disease (12).

In the meantime, the long-term renal outcomes favoring the fish oil group in this study indicate that early and prolonged treatment with fish oil retards renal progression for high-risk patients with IgA nephropathy.

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Appendix

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