

Use of fish oil to treat patients with immunoglobulin A nephropathy¹⁻³

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ABSTRACT This review describes the use of fish oil in the treatment of patients with immunoglobulin (Ig) A nephropathy. IgA nephropathy is the most common glomerular disease worldwide. It has a variable course and leads to end-stage renal disease in a substantial number of cases. Among the 4 published randomized clinical trials that tested the efficacy of fish-oil treatment of IgA nephropathy, 2 reported beneficial effects on renal function and 2 showed negative results. In the largest trial conducted by my collaborative study group, convincing evidence was provided for protection against progressive renal disease after daily treatment for 2 y with fish oil providing 1.8 g eicosapentaenoic acid and 1.2 g docosahexaenoic acid—the 2 major n-3 polyunsaturated fatty acids in fish oil. Oral prednisone has also been advocated, especially in the treatment of children with IgA nephropathy. Two randomized trials are currently underway in the United States to resolve the discrepancy of results in previous fish-oil trials and to determine whether corticosteroids or fish oil is the better treatment of patients at risk for developing progressive disease; results of these studies are not yet available. *Am J Clin Nutr* 2000;71(suppl):373S–5S.

KEY WORDS Immunoglobulin A nephropathy, treatment, fish oil, renal disease

INTRODUCTION

Immunoglobulin (Ig) A nephropathy is the most common glomerular disease worldwide (1, 2). Progressive renal failure develops up to 25 y after diagnosis in 20–40% of patients, although there is considerable variability in the clinical course of different groups of patients (3–6). IgA nephropathy is an immune complex glomerulonephritis caused by the mesangial deposition of IgA immune complexes, but the pathogenesis beyond this point is poorly understood (7). Important predictors of progression are hypertension, proteinuria, impaired renal function at diagnosis, high total histopathologic scores, and features of glomerulosclerosis and interstitial fibrosis (8, 9).

The variable rate of progression and likely multifactorial pathogenesis of IgA nephropathy make it difficult to show the effectiveness of any treatment. Despite initial claims of success, most interventions have proven to be ineffective in controlled trials. Among the therapies offered, prednisone and fish oil have produced the most encouraging results.

The use of alternate-day prednisone in children (10) and daily prednisone in adults (11) has been shown to stabilize glomerular filtration rate (GFR) in children and to prolong renal functioning in adults compared with non-steroid-treated patients when initial renal function was normal. However, results from 3 controlled trials of prednisone have shown no benefits (K Nicholls, P Kincaid-Smith, G Becker, unpublished observations; 12, 13). Each of these trials involved small numbers of patients who were followed for short periods of time (≤ 12 mo).

The efficacy of fish oil was reported in 4 randomized studies with varying results. The rationale for using fish oil in IgA nephropathy is based on the premise that n-3 polyunsaturated fatty acids (PUFAs) may limit the production or action of cytokines and eicosanoids evoked by the initial or by repeated immunologic renal injury, thereby influencing mediators involved in renal damage (14). This review describes the findings of the 4 clinical trials of treatment with fish oil (15–18) and compares the changes in renal function observed between fish-oil- and placebo-treated patients in my groups's trial (18) with those found in other cohorts of patients with IgA nephropathy [in Sweden (19) and Canada (20)] who were not treated with fish oil.

Clinical trials of treatment with fish oil

Of the 4 randomized clinical trials, 2 showed that fish oil stabilized renal function and 2 reported a decline in renal function (**Table 1**). The findings of the largest study, which comprised 106 patients and was conducted by my collaborative group, provided strong evidence that in patients with persistent proteinuria >1 g/24 h and deteriorating renal function (serum creatinine <265 $\mu\text{mol/L}$ at study entry), treatment for 2 y with a daily 12-g dose of fish oil stabilized renal function (18). In the study from Japan, renal function did not deteriorate in 9 patients who were treated with fish oil for 1 y but did decline in 11 who were untreated (15). The 6-mo follow-up period of the Swedish study may have been too short to show an effect because the changes in renal function were statistically significant although small and of little clinical significance (17). In the Australian trial, no benefit of

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TABLE 1Fish-oil treatment of patients with immunoglobulin A nephropathy reported in randomized clinical trials¹

| Geographic location | Trial conditions | | |
|--------------------------------------|------------------|-----------------------|------------------------|
| | EPA, DHA | Duration of treatment | Renal function outcome |
| | <i>g/d</i> | <i>y</i> | |
| Japan (15) (<i>n</i> = 20) | 1.6, 1.0 | 1 | Stabilized |
| Australia (16) (<i>n</i> = 37) | 1.8, 1.2 | 2 | Declined |
| Sweden (17) (<i>n</i> = 32) | 3.3, 1.8 | 0.5 | Declined |
| North America (18) (<i>n</i> = 106) | 1.8, 1.2 | 2 | Stabilized |

¹EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

fish oil was seen. The study design was similar to ours but included only 37 patients and made no mention of the number of hypertensive subjects or of how they were managed (16). Hypertension is an important risk factor associated with progressive renal disease (8, 9).

Changes in renal function in different patient groups with IgA nephropathy

A major criticism leveled at our study is that the placebo-treated group did particularly poorly, raising the possibility of selection bias favoring the actively treated group (21). The 2 treatment groups in the study were well matched in all categories (18). Also, the difference between treatments, which showed a favorable influence on renal function of the fish oil in treated patients, remained significant after adjustment for the 3 stratification factors, which were hypertension, impaired renal function, and nephrosis-range proteinuria (18). These clinical variables are well recognized, important predictors of progressive renal failure (3–6, 8, 9).

Serial changes in renal function can be compared between fish-oil- and placebo-treated patients enrolled in our clinical trial (18)

TABLE 2

Annualized changes in estimated glomerular filtration rate (GFR) in different patient groups with immunoglobulin A nephropathy

| Study | GFR change ¹ <i>mL·min⁻¹·y⁻¹</i> |
|--|--|
| Stockholm (19) | |
| All patients (<i>n</i> = 153) | -1.4 |
| Males (<i>n</i> = 106) | -2.5 |
| Advanced histology (<i>n</i> = 48) | -3.4 |
| Proteinuria | |
| >1 g/24 h (<i>n</i> = 72) | -3.6 |
| >3.5 g/24 h (<i>n</i> = 11) | -8.8 |
| Hypertensive (<i>n</i> = 68) | -4.0 |
| Toronto Glomerulonephritis Registry (20) | |
| Normotensive (<i>n</i> = 33) | -6.0 |
| Hypertensive | |
| Treated with ACEI ² (<i>n</i> = 27) | -8.4 |
| Treated with other antihypertension drugs (<i>n</i> = 55) | -12.0 ³ |
| Mayo Collaborative Group (18) | |
| Placebo treated (<i>n</i> = 51) | -7.1 |
| Fish-oil treated (<i>n</i> = 55) | -0.3 ⁴ |

¹Average annual slopes of ⁵¹CrEDTA clearance for ≥1 y in Stockholm patients and median annual slopes of creatinine clearance in Toronto patients for ≥3 mo and in American patients for ≥2 y.


²ACEI, angiotensin-converting enzyme inhibitor.

³Significantly different from group treated with ACEI, *P* < 0.05.

⁴Significantly different from placebo-treated group, *P* < 0.01.

and with changes in renal function reported in 2 cohorts of patients with IgA nephropathy from Sweden (19) and Toronto (20) who were not treated with fish oil (Table 2). The placebo-treated group in our trial showed a declining rate of renal function similar to that observed in high-risk Swedish patients (with advanced histology, high-grade proteinuria, and hypertension) and similar to that in both normotensive and hypertensive Canadian patients. The hypertensive Canadian patients who were treated with angiotensin-converting enzyme inhibitors, drugs that are promoted as protectors of renal function in proteinuric glomerulopathies such as IgA nephropathy (20, 22), also showed declining renal function. Furthermore, the annual decreases in GFR were much greater in all of these groups than in the fish-oil-treated group, which provides additional evidence for the favorable effects of fish-oil treatment in stabilizing renal function.

Studies of fish oil in the treatment of patients with IgA nephropathy: in progress

In an effort to resolve the discrepancy in results in the 4 clinical trials (Table 1) and the issue of which is the better treatment for patients at risk of developing progressive disease, corticosteroids or *n*-3 fatty acids, 2 prospective studies are currently underway in the United States. The first trial tests the hypothesis that alternate-day prednisone or daily fish oil will retard the decline in renal function in children and young adults with moderate IgA nephropathy (23). The study design is a randomized, placebo-controlled, multicenter trial conducted by the North American IgA Nephropathy Study Group and includes patients of both pediatric and internal medicine nephrologists. The second trial is testing the hypothesis that relatively large amounts of *n*-3 fatty acids will influence clearly progressive IgA nephropathy (JV Donadio Jr, EJ Bergstralh, KP Offord, DC Spencer, JP Grande for the Mayo Nephrology Collaborative Group, unpublished observations, 1999). The study is an open-label, comparative dose design using Omacor (Pronova Biocare, Lysaker, Norway), a highly concentrated form of *n*-3 PUFAs, that is being conducted by our collaborative group. Both of these trials are 4-y studies, and because patients were entered into them beginning in late 1995, results are not yet available. 

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