

n-3 Fatty acid supplements in rheumatoid arthritis^{1,2}

Joel M Kremer

ABSTRACT Ingestion of dietary supplements of n-3 fatty acids has been consistently shown to reduce both the number of tender joints on physical examination and the amount of morning stiffness in patients with rheumatoid arthritis. In these cases, supplements were consumed daily in addition to background medications and the clinical benefits of the n-3 fatty acids were not apparent until they were consumed for ≥ 12 wk. It appears that a minimum daily dose of 3 g eicosapentaenoic and docosahexaenoic acids is necessary to derive the expected benefits. These doses of n-3 fatty acids are associated with significant reductions in the release of leukotriene B₄ from stimulated neutrophils and of interleukin 1 from monocytes. Both of these mediators of inflammation are thought to contribute to the inflammatory events that occur in the rheumatoid arthritis disease process. Several investigators have reported that rheumatoid arthritis patients consuming n-3 dietary supplements were able to lower or discontinue their background doses of nonsteroidal antiinflammatory drugs or disease-modifying antirheumatic drugs. Because the methods used to determine whether patients taking n-3 supplements can discontinue taking these agents are variable, confirmatory and definitive studies are needed to settle this issue. n-3 Fatty acids have virtually no reported serious toxicity in the dose range used in rheumatoid arthritis and are generally very well tolerated. *Am J Clin Nutr* 2000;71(suppl):349S-51S.

KEY WORDS n-3 Fatty acids, rheumatoid arthritis, fish oil, inflammation, eicosapentaenoic acid, docosahexaenoic acid

INTRODUCTION

Our appreciation of the possible role of nutritional manipulation in the treatment of inflammatory disease has increased along with our understanding of immunity, eicosanoid metabolism, and cellular biology. Although it has been known for some time that disease processes can interfere with adequate nutrition, we are only now beginning to understand how altered nutritional status may contribute to or alter the pathogenesis of disease. These principles represent an evolution of thinking from the relatively recent past, when contributors to the field of inflammation believed it extremely unlikely that dietary manipulation could affect patients in any way.

n-3 Fatty acids are given as dietary supplements to patients who have rheumatoid arthritis, the most common systemic inflammatory rheumatic disease. These supplements are consumed while patients continue to take their background medications, such as slow-acting, antirheumatic drugs and nonsteroidal

antiinflammatory drugs (NSAIDs). Most studies of n-3 fatty acid supplementation use fatty acids in the triacylglycerol form, although ethyl esters of fatty acids have also been studied. Although there are some conflicting data on the absorption of the ethyl ester compared with the triacylglycerol (1, 2), most investigators believe that there is little practical difference in tolerability or efficacy between these 2 formulations. Some investigators advocate use of a free fatty acid formulation (in which there is no linkage to a glycerol or an ester), although, to date, no studies in humans with rheumatoid arthritis have used this formulation.

ANIMAL STUDIES

Certain inbred strains of mice develop spontaneous autoimmune disease and have been used as models to study the effects of dietary intervention. NZB \times NZW F1 MRL lpr and B \times SB/Mjpr strains all develop diffuse glomerulonephritis as well as serologic and clinical features akin to human systemic lupus erythematosus. In trials reported >10 y ago, dietary supplementation with marine lipids significantly ameliorated disease activity in these animals (3, 4). Not all animal studies of dietary supplementation with n-3 fatty acids have resulted in beneficial effects: type II collagen-induced arthritis worsened in animals fed fish oil compared with those fed beef tallow (5). Interestingly, recent studies of purified eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) indicate that the mixture of these 2 major n-3 fatty acid constituents of fish oil may be more effective than either fatty acid by itself (6).

HUMAN STUDIES

Several investigators have studied the effects of dietary fish-oil supplements in patients with rheumatoid arthritis. Studies of predominantly white subjects of northern European background have been reported from the United States (7-11), Australia (12), and Europe (13-19). It is unlikely that background dietary habits were uniform in these populations, however. Some populations were known to consume more fish oil in their diet (16) than others (20). The benefit most often observed with fish-oil supplementation is an improvement in the number of tender joints on

¹From the Division of Rheumatology, Albany Medical College, New York.

²Address reprint requests to JM Kremer, Division of Rheumatology, Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208.

physical examination (8, 10–15), although some authors reported improvement in the Ritchie Articular Index (15, 18) and in morning stiffness (10, 12, 15). *n*-3 Fatty acid supplements have been studied in comparison with a variety of dietary interventions, including inert paraffin wax (7), corn oil (11, 15), olive oil (8–10), and a specially prepared mixture of fatty acids designed to reproduce local dietary intake (16–18). Improvements in the number of tender joints and in morning stiffness were confirmed in a meta-analysis of published studies that used a wide range of daily dietary supplementation with *n*-3 fatty acids (21).

It is accurate to portray the overall clinical response to fish-oil supplements in these investigations as modest (22, 23). However, it is clear that dietary fatty acids effect reproducible alterations in eicosanoid metabolism that should aid in the amelioration of inflammation (8, 9, 12, 24–26). In addition, fish-oil supplements are associated with decreased production of interleukin 1 β in healthy humans (27) and in patients with rheumatoid arthritis (8, 10). It is the unique ability of dietary fatty acids to alter the fatty acid constituents of cell membranes (22) that has generated interest in the potential of the highly polyunsaturated fatty acids to influence an array of immune variables.

We were interested in expanding our observations of the beneficial effects of fish oil in patients with rheumatoid arthritis to determine whether patients consuming high-dose supplements would be better able to discontinue use of NSAIDs than would a control population given corn oil (11). Forty-nine patients taking the NSAID diclofenac were studied in a prospective, double-blind investigation. Patients randomly assigned to receive fish oil ingested 130 mg *n*-3 fatty acids \cdot kg⁻¹ \cdot d⁻¹ (ethyl ester concentrate prepared by the National Institutes of Health, Bethesda, MD) while control patients consumed corn oil capsules. After 18–22 wk, all patients were given placebo diclofenac but continued their respective fatty acid supplements for another 8 wk, at which time all patients were given corn oil. Clinical evaluations were performed for several months after diclofenac treatment was discontinued and also after the fish-oil supplements were stopped. Several cytokines were measured throughout the study, including interleukins 1, 2, 6, and 8 and tumor necrosis factor α .

We found a significant reduction in the number of tender joints and improvements in other clinical variables of disease over 18–22 wk from baseline in the patients who consumed dietary supplements of fish oil while taking diclofenac (11). However, none of the improvements in the patients receiving fish oil were significantly different at the time of the maximum duration of diclofenac therapy (at 18 or 22 wk) from the improvements in patients receiving corn oil. Patients receiving corn oil tended to have fewer swollen joints during this time interval than at baseline. In addition, the magnitude of the improvement from baseline observed in patients receiving high doses of fish oil was indistinguishable from that reported previously when patients consumed total *n*-3 fatty acid dosages of 3–6 g/d (8, 10). We cannot, therefore, recommend further investigations with the dosages we used, which resulted in the ingestion of 9 g *n*-3 fatty acids/d by a 70-kg person, because it appears that dietary supplements containing 3–6 g *n*-3 fatty acids are sufficient.

Improvements from baseline in rheumatoid arthritis patients consuming fish oil are often not significantly different from improvements in patients receiving other dietary fatty acid interventions. This may be either because the biological effects are not powerful enough or because of a placebo effect—real biological effects induced by the so-called placebo

fatty acids. We previously wrestled with the issue of an ideal control fatty acid to compare with fish oil (10) and chose corn oil in our most recent investigation (11) after using olive oil (8, 10). It is possible that any mono- or polyunsaturated fatty acid has significant potential immune effects. We believe that the issue of the ideal placebo dietary intervention to compare with fish oil in the study of autoimmune inflammatory disease has not yet been settled.

We examined the clinical status of patients after they had stopped receiving diclofenac but continued to receive fish oil or corn oil in several ways (11). We examined clinical status after the discontinuation of diclofenac and the maximal duration of fish-oil exposure (week 26 or 30) and compared this with baseline status while patients were receiving diclofenac. The improvement in the number of tender joints was significant in the patients continuing to receive fish-oil treatment compared with both baseline status and with patients receiving corn oil during the same period. We observed a significant decrease in interleukin 1, confirming our previous observations (8, 10), but did not find significant decreases in interleukins 2, 6, or 8 or tumor necrosis factor α .

Others have investigated whether dietary fish-oil supplements can affect NSAID requirements in patients with rheumatoid arthritis. Skoldskam et al (14) used open, patient-directed reduction of NSAID use and found that patients consuming fish oil could significantly reduce their NSAID dose compared with a control group. In this study, patients lowered or discontinued their use of NSAIDs in an open manner although they were blinded to the dietary supplement consumed. Belch et al (17) used open, physician-directed reduction of NSAID use while subjects consumed 240 mg EPA and 450 mg γ -linolenic acid daily and found that, after 1 y, NSAID doses could be reduced significantly (17). In another study, Kjeldsen-Kragh et al (15) substituted placebo naproxen for the real drug in a stepwise manner. In this open study, the investigators were aware that 2 of 3 treatment groups would be discontinuing naproxen treatment. Nevertheless, they reported that patients receiving fish oil tolerated discontinuation of the NSAID better than did patients receiving corn oil. Finally, Lau et al (28) reported that patients receiving fish oil could significantly reduce their NSAID dose compared with that of a control group. We believe our data (11) support these observations that selected individuals with rheumatoid arthritis can discontinue or reduce NSAID therapy while consuming *n*-3 fatty acid supplements.


OTHER INFLAMMATORY CONDITIONS

Subsequent to the reports of the benefits of fish-oil supplementation in patients with rheumatoid arthritis, *n*-3 fatty acid supplements have been used with some reported benefit in patients with inflammatory bowel disease (29) and immunoglobulin A nephropathy (30). Many other inflammatory conditions may benefit from the *n*-3 fatty acid-induced changes in eicosanoid metabolism and decreased production of interleukin 1 described above.

CONCLUSIONS

On the basis of the totality of the data, it is recommended that patients consume dietary supplements containing 3–6 g *n*-3 fatty acids daily for \geq 12 wk. The dietary supplement should not replace the standard therapeutic medical regimen, but be added to it. Note, however, that there are many forms of



arthritis and that clinical studies demonstrating efficacy have been performed only in patients with rheumatoid arthritis. After taking n-3 fatty acid dietary supplements for 3-4 mo, patients may try reducing their NSAID dose under the supervision of a physician. 

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