

Polyunsaturated fatty acids and inflammatory bowel disease^{1,2}

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ABSTRACT The rationale for supplementation with n-3 fatty acids to promote the health of the gastrointestinal tract lies in the antiinflammatory effects of these lipid compounds. The first evidence of the importance of dietary intake of n-3 polyunsaturated fatty acids was derived from epidemiologic observations of the low incidence of inflammatory bowel disease in Eskimos. The aim of this paper was to briefly review the literature on the use of n-3 fatty acids in inflammatory bowel disease (ulcerative colitis and Crohn disease), the results of which are controversial. The discrepancies between studies may reside in the different study designs used as well as in the various formulations and dosages used, some of which may lead to a high incidence of side effects. Choosing a formulation that lowers the incidence of side effects, selecting patients carefully, and paying strict attention to experimental design are critical when investigating further the therapeutic potential of these lipids in inflammatory bowel disease. *Am J Clin Nutr* 2000; 71(suppl):339S-42S.

KEY WORDS Polyunsaturated fatty acids, fish oil, Crohn disease, ulcerative colitis, inflammatory bowel disease, n-3 fatty acids, review

INTRODUCTION

n-3 Fatty acids have been suggested as a treatment for various chronic inflammatory conditions, including inflammatory bowel disease, because of their antiinflammatory properties. This effect may be mediated by a lower production of the most powerful arachidonic acid metabolite, leukotriene B₄ (1), which is elevated in the inflamed intestinal mucosa (2), as well as by a reduction in another arachidonic acid metabolite, thromboxane A₂, which is released even in uninflamed mucosa in inflammatory bowel disease—an early abnormality of special pathogenic significance (3). It has also been shown that n-3 fatty acids can inhibit interleukin 1 β , inhibit tumor necrosis factor production (4), and possibly act as free radical scavengers (5). Moreover, multifocal gastrointestinal infarctions have been suggested as one of the first pathogenic steps in Crohn disease (CD) (6), which suggests that platelets and possibly the powerful platelet aggregator thromboxane A₂ may play a pivotal role in this process (7). Treatment with n-3 fatty acids has been shown to decrease platelet responsiveness in patients with inflammatory bowel disease (8).

CLINICAL STUDIES

In an uncontrolled study, McCall et al (9) treated 6 patients with active ulcerative colitis (UC) with 3–4 g eicosapentaenoic acid (EPA)/d (16–24 capsules of fish oil as triacylglycerol) for 12 wk and reported a significant improvement in symptoms and histologic appearance, along with a significant decrease in leukotriene B₄ neutrophil production. In 1990, Salomon et al (10), in another uncontrolled study, treated 10 UC patients who were refractory to conventional treatment (steroids and salicylates) with 2.7 g EPA/d and 1.8 g docosahexaenoic acid (DHA)/d (15 capsules of fish oil as triacylglycerol) for 8 wk. All of the measures of disease activity (whether the disease was active or in remission) improved significantly in 7 patients; in 3 patients there was little or no improvement.

Lorenz et al (11) treated 29 CD patients in different stages of clinical disease activity and 10 UC patients with active disease in a 7-mo, controlled, crossover trial. Patients received 3.2 g n-3 fatty acids/d and olive oil as a placebo while conventional treatment was continued. The washout period was 1 mo. Encouraging positive results were obtained in the UC patients, whereas the activity score of the disease did not improve in the CD patients.

In 1992, Hawthorne et al (12) published the first large placebo-controlled study of n-3 fatty acids and inflammatory bowel disease. In this study, 96 UC patients in different activity stages of the disease were enrolled and assigned to receive either 4.5 g EPA/d as triacylglycerol (treatment group) or olive oil (placebo group) for 1 y. Conventional treatment was allowed to continue in both groups. In patients with active disease at entry, a significant steroid-sparing effect of fish oil was shown, but fish oil did not affect the predicted endpoint, ie, the prevention of clinical relapse in the group of patients enrolled while their disease was in remission. Remarkably, leukotriene B₄ production in stimulated neutrophils was reduced by >50% in the treatment group.

Stenson et al (13) carried out a randomized, double-blind, placebo-controlled crossover study with 5.4 g n-3 fatty acids as triacylglycerol (18 capsules daily) or olive oil as the placebo in 24 patients with active UC. Patients received the

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treatment for 4 mo followed by a washout period lasting 1 mo. In this study, fish-oil treatment induced significant body weight gain, significantly improved the histology score, and reduced leukotriene B₄ production in rectal dialysates by 60%. No significant steroid-sparing effect of fish oil compared with placebo was found, however, and the endoscopy score was not significantly improved ($P = 0.06$).

Aslan and Triadafilopoulos (14) carried out a similar placebo-controlled, crossover trial by giving 4.2 g n-3 fatty acids/d or corn oil as the placebo. Seventeen patients with active UC received the treatment for 3 mo followed by a washout period lasting 2 mo. A steroid-sparing effect of n-3 fatty acids was observed in 72% of patients, and in 56% of patients the activity score of the disease improved significantly. Improvements in the histology score were not significant.

Matè et al (15) reported preliminary data on a group of 38 CD patients in clinical and laboratory remission characterized by a Crohn's Disease Activity Index <150. The patients were randomly assigned to receive either a diet enriched with fish (from 100 to 250 g fish/d) or a regular diet for 2 y. Symptomatic remission of the disease was longer in those who received the enriched diet.

More recently, Loeschke et al (16) presented data from a placebo-controlled trial of prevention of UC relapse. Sixty-four patients with disease in remission were randomly assigned to receive 5.1 g n-3 fatty acids as ethyl esters or corn oil as a placebo daily for 2 y. Ongoing treatment with 5-aminosalicylic acid was allowed for 3 mo. Interestingly, after 3 mo, the fish-oil group had experienced fewer relapses than did the placebo group ($P < 0.02$) but this beneficial effect did not last until the end of the study (2 y). We can speculate that the fish oil and the 5-aminosalicylic acid had synergetic effects; however, we cannot rule out the possibility that compliance decreased over time in the fish-oil group, which would have affected the clinical outcome.

Lorenz-Meyer et al (17) published data from a large, placebo-controlled trial in which 204 CD patients recovering from an acute relapse were randomly assigned to receive n-3 fatty acids ($n = 70$; 5.1 g/d as ethyl esters), a diet poor in carbohydrate ($n = 69$), or a placebo ($n = 65$) for 1 y. Low doses of prednisolone were allowed for 8 wk. In an intent-to-treat analysis, none of the treatments prevented clinical flare-ups, but in the per-protocol analysis the diet poor in carbohydrate (20 dropouts) seemed to be effective ($P < 0.05$). It is important to stress that >60% of patients treated with steroids after an acute relapse have further relapses at 6 mo, after steroid treatment is suspended (18).

The crossover design of most of these studies, with short washout periods between the 2 treatments, did not allow for a complete displacement of the extra n-3 fatty acids from the membrane, which may have interfered with the final results. Endres et al (4) showed that the inhibition of cytokine production lasts for >10 wk after the suspension of supplementation with n-3 fatty acids.

PLACEBO EFFECTS

The choice of placebo is another crucial consideration in studies of n-3 fatty acids and inflammatory bowel disease because it has been shown that olive oil exerts some important beneficial effects, such as free radical scavenging (19) and inhibition of eicosanoid formation (20). Even corn oil is a rich source of linoleic acid, an essential n-6 fatty that is desaturated and elon-

gated to dihomo- γ -linolenic acid, a precursor of the 1-series of prostanoids that may have antiinflammatory properties in many chronic inflammatory disorders (21).

Moreover, in many of the studies in which fish oil was used, patient compliance was poor (22–24). This poor compliance was caused by the poor palatability of the diets and by minor but annoying side effects such as halitosis, belching, and diarrhea resulting from the high daily intake of fish-oil preparations, which is necessary for satisfactory intestinal absorption and incorporation of n-3 fatty acids into membranes.

We carried out a study of patient tolerance in a group of CD patients with a new n-3 fatty acid preparation that consisted of 500 mg enteric-coated (gastric resistant) capsules of EPA (40%) and DHA (20%) as a free fatty acid mixture. This was compared with a traditional preparation of n-3 fatty acids as triacylglycerol. In addition to patient tolerance, we evaluated the incorporation of the n-3 fatty acids into phospholipids in plasma and red blood cell membranes. The new preparation showed the best incorporation of EPA and DHA in red blood cell phospholipid membranes and had no associated side effects (25).

We also performed a 1-y, double-blind, placebo-controlled study to investigate the effect of this new formulation in 78 CD patients who had a high risk of relapse (26). Patients with a well-established diagnosis of CD in clinical remission were evaluated for eligibility for this study according to the Crohn's Disease Activity Index. This index incorporates 8 items—the daily number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestations of CD, use of opiates to treat diarrhea, abdominal mass, hematocrit, and body weight—to yield a composite score ranging from 0 to 600. Higher scores indicate more disease activity. Patients with scores of ≤ 150 are considered to have inactive disease. The main eligibility criteria for our study were a Crohn's Disease Activity Index <150 for ≥ 3 mo but <2 y and ≥ 1 of the following: serum $\alpha 1$ acid glycoprotein >1.3 g/L (reference range: <1.2 mg/L), serum $\alpha 2$ globulin >9 g/L (reference range: <8 g/L), erythrocyte sedimentation rate >40 mm/h (reference range: <20 mm/h). Patients received either 9 capsules containing a total of 2.7 g n-3 fatty acids or 9 placebo capsules (a mixture of capric and caprylic acids) daily. A special coating protected the capsules against acidity for ≥ 30 min. Of the 39 patients in the n-3 fatty acid group, 11 (28%) had relapses, 4 dropped out because of diarrhea, and 1 withdrew from the study. In contrast, of the 39 patients in the placebo group, 27 (69%) had relapses, 1 dropped out because of diarrhea, and 1 withdrew from the study ($P < 0.001$). After 1 y, 23 patients (59%) in the n-3 fatty acid group remained in remission compared with 10 (26%) in the placebo group ($P = 0.003$). The Kaplan-Meier life-table curves for patients remaining in clinical remission are shown in **Figure 1**. Logistic regression analysis indicated that only n-3 fatty acids and not sex, age, previous surgery, duration of disease, or smoking status affected the likelihood of relapse (26).

Only one placebo-controlled study of the use of n-6 fatty acids in patients with UC has been performed. Greenfield et al (27) compared the effectiveness of evening primrose oil, which is rich in γ -linolenic acid and linoleic acid, with that of n-3 fatty acids and olive oil in 43 patients with UC in different phases of activity. The patients' normal treatments were continued. After 6 mo, no beneficial effects were shown in the patients taking evening primrose oil except for an increase in stool consistency.

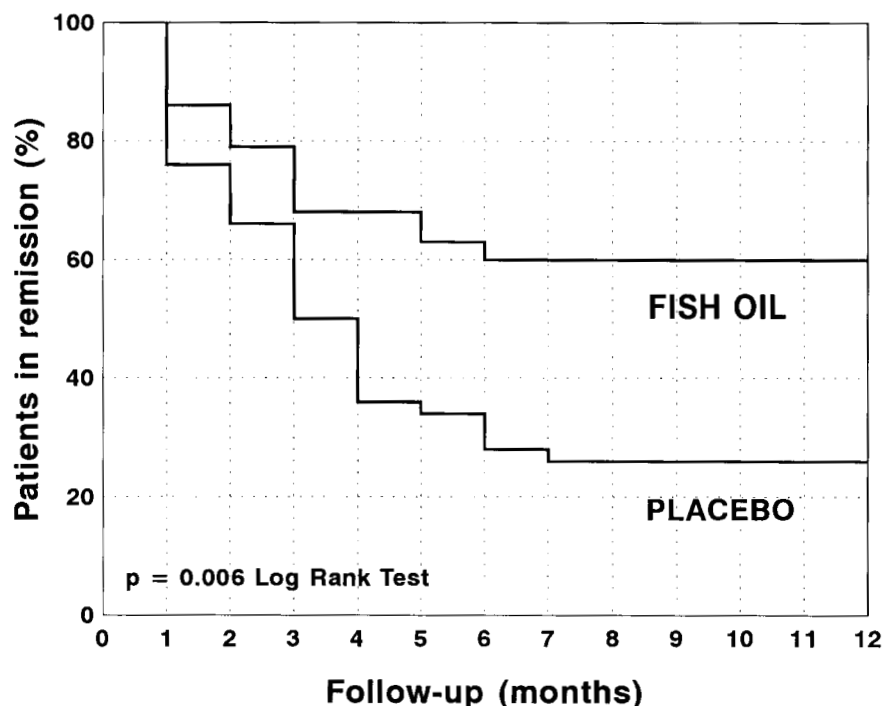



FIGURE 1. Kaplan-Meier life-table curves showing the percentage of patients remaining in clinical remission during the treatment period. Reprinted from reference 26. Copyright 1996 Massachusetts Medical Society. All rights reserved.

CONCLUSION

In conclusion, this overview indicates a potential effectiveness of n-3 fatty acids in the therapy of CD and UC. The conflicting results reported can be ascribed to differences in study design (such as patients selection, influence of concomitant therapy, and choice of placebo) as well as to different formulations of the fatty acids, which have been shown to influence not only the delivery and absorption of the fatty acids but also patient compliance. The administration of lower doses of new formulations of free fatty acids may reduce side effects and improve the therapeutic potential of n-3 fatty acids, offering a new perspective in the management of inflammatory bowel disease. 

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