Polyunsaturated fatty acids (n-3 PUFAs) and inflammatory bowel disease (IBD): pathogenesis and treatment

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Abstract. – There is considerable evidence to suggest that polyunsaturated fatty acids (PUFAs) alleviate a number of inflammatory diseases, mainly the fish derivatives, n-3 PUFAs. My aim is to briefly review the literature involving clinical interventions with these lipid compounds in the treatment of Ulcerative Colitis (UC) and Crohn’s Disease (CD), Inflammatory Bowel Disease (IBD). Data available are conflicting and the reason for the discrepancies in the findings could reside in the different study designs. Often studies are limited by the choice of placebo and insufficient washout period and direct comparison of trials is hampered by the use of various formulations and dosages of n-3 PUFAs.

The importance of the n-3 PUFAs formulation in lowering the incidence of side effects along with careful selection of patients and experimental design seems to be associated with benefits. It is possible these fatty acids act by reducing low-grade active inflammation rather than by preventing reinitiation of the inflammatory process from a truly quiescent state. Whether this treatment is applicable to all patients with IBD has not been fully elucidated. Nevertheless, taken together, all these studies suggest the effectiveness of these new therapeutic approaches, not only when the conventional treatment fails or it is not possible to treat chronically, but also, in some instances as first choice.

Key Words: IBD, Crohn’ disease, Ulcerative colitis, Fish oil, n-3 PUFAs.

Background

Over the last few years a growing body of evidence has demonstrated that n-3 PUFAs alleviate a number of inflammatory diseases. This work stems for the early epidemiological observation that high dietary intake of these lipids was associated with a very low incidence of chronic inflammatory conditions in Eskimos. Dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major components of fish oil, partially replace arachidonic acid (AA) in a time and dose dependent manner in plasma and cellular phospholipids. These are less readily released upon cell stimulation and reduce the availability of AA for eicosanoid generation. In addition, the n-3 PUFAs reduce the production of the 2-series eicosanoids generated by AA metabolism that are all pro-inflammatory. These include leukotriene B₄ (LTB₄), the most potent chemotactic agent which is responsible of neutrophil recruitment, as well as thromboxane A₂ (TXA₂) which is deeply involved in the inflammatory process by increasing vascular permeability, promoting platelet aggregation and causing oedema. In addition, n-3 PUFAs reduce the production of the 2-series eicosanoids generated by AA metabolism that are all pro-inflammatory. These include leukotriene B₄ (LTB₄), the most potent chemotactic agent which is responsible of neutrophil recruitment, as well as thromboxane A₂ (TXA₂) which is deeply involved in the inflammatory process by increasing vascular permeability, promoting platelet aggregation and causing oedema. In addition, n-3 PUFAs serve as precursors to a class of eicosanoids with limited inflammatory properties, such as leukotriene B₄ (LTB₄). It has also been widely demonstrated that n-3 fatty acids, such as EPA and DHA, are able to inhibit inflammatory cytokine production. Cytokines such as interleukin-1 β, interleukin-2, interleukin-6 and tumor necrosis factor (TNF-α), belong to a class of soluble proteins that influence the immune cell system resulting in enhancement of production of chronic inflammatory substances.6,7, Evenmore Grimble et al. have recently demonstrated that the ability of fish oil to decrease TNF-α production is influenced by inherent TNF-α production and by polymorphisms in the TNF-α and lymphotoxin alfa gene. N-3 PUFAs may also act as free-radical scavengers.
Moreover, multifocal gastrointestinal infarctions have been suggested as one of the first pathogenic steps in IBD, thus suggesting a pivotal role for platelets, as underlined recently by recent observations, and possibly for the powerful platelet aggregator thromboxane A2; treatment with n-3 PUFAs has been shown to decrease platelet responsiveness in patients with IBD.

It has also been demonstrated that fish oil supplementation improves the nutritional state of rats in which a short bowel syndrome, a clinical condition that may also affect CD patients after multiple surgical bowel resections, was induced. These results were obtained by inducing enterocyte hyperplasia, which markedly increases the mucosal surface area with a corresponding increase in enteral absorption. In this respect, it has recently been shown that increasing dietary polyunsaturated fat intake in IBD patients enhances by 65% the absorption and the utilisation of saturated fat, such as palmitic acid, improving the overall nutritional condition.

**n-3 PUFAs Trials**

Investigation of n-3 PUFAs in inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease (CD), began at the end of the eighties. Shoda et al. provided epidemiological evidence relating to the incidence of IBD in Japan. They showed that increasing incidence of CD was strongly correlated with, among others, the ratio of n-6 to n-3 fatty acid intake (r = 0.792) where increased dietary intake of n-6 with less n-3 PUFAs, may contribute to the development of CD.

From the clinical point of view, the first evidence of clinical benefit came from McCall who, in an open study, treated 6 patients with active UC by giving 3-4 g of EPA daily (16-24 capsules of fish oil as triacylglycerol) for 12 weeks and obtained a significant improvement in symptoms and in histological appearance, along with a significant fall in leukotriene B4 production.

The first prospective, controlled and double blind study was published by Lorenz et al. who treated 39 patients with IBD, of which 29 had CD, in different stages of clinical activity in a 7-month controlled, crossover trial. Patients were randomised to receive either 3.2 g daily of n-3 PUFA or olive oil as placebo. Conventional treatment was discontinued whenever possible. Otherwise it was minimized and kept constant for at least 3 weeks before the study and until completion. Between the two treatments there was a one-month wash out-period. At the end of the study, the clinical activity expressed by Crohn’s Disease Activity Index (CDAI) was unchanged in patients with CD after n-3 PUFA s supplementation.

Hawthorne et al. published the first large placebo controlled study in 1992. In this study 96 UC patients in different activity stages were enrolled and were given 4.5 g daily of EPA as triacylglycerol for 1 year. The patients in the placebo group received olive oil. In patients with active disease at entry, it was possible to demonstrate a significant steroid sparing effect, but fish oil failed to prevent clinical relapse in the group of patients enrolled in remission. Remarkably, the leukotriene B4 production in stimulated neutrophils was reduced by more than 50%.

Stenson et al. carried out a randomised double-blind placebo-controlled crossover study with 5.4 g of n-3 PUFA as triacylglycerol (18 capsules daily), or olive oil as placebo, in 24 active UC patients. The patients received treatment for 4 months followed by 1 month of washout. The study demonstrated that fish oil was able to induce a significant gain in body weight, significantly improve the histology score and reduce the leukotriene B4 production in rectal dialysates by 60%. No significant steroid sparing effect was found compared with placebo and the improvement in the endoscopy score did not reach a significant level (p = 0.06). A slan and Tridafilopoulos carried out a similar placebo-controlled crossover trial by giving 4.2 g of n-3 PUFA daily or corn oil as placebo. Seventeen active UC patients received treatment for 3 months followed by 2 months of wash-out. In 72% of patients, a steroid sparing effect was seen and in 56% the activity score of the disease improved significantly. Improvement of the histology score did not reach statistical significance.

More recently Loeschke et al. presented data on a placebo-controlled trial in the prevention of UC relapse. 64 patients in remission were randomised to receive 5.1 g of n-3 PUFA s as ethyl-esters or maize oil as placebo.
for 2 years. The ongoing treatment with 5-aminosalicylic acid was allowed for 3 months. Interestingly after 3 months of study, the fish oil group had fewer relapses than the placebo group ($p < 0.02$) but this beneficial effect was lost by the end of the study (2 years). This leads to speculation that fish oil and 5-aminosalicylic acid may have synergetic effects and also that patient compliance in the fish oil group decreased during the study and could have affected the clinical outcome.

Lorenz-Meyer et al.\textsuperscript{24} published data from a large, placebo-controlled trial in 204 CD patients. Patients were included after an acute relapse of their disease in which remission (CDAI < 150) was obtained under steroid therapy. Patients were randomised to receive either n-3 PUFA (n = 70) (5.1 g daily of fish oil as ethyl-esters), a carbohydrate-reduced diet, (72 g/daily) (n = 69) or placebo (corn oil) (n = 65) for 1 year. Low dose prednisolone was given to all patients for the first 8 weeks of the trial and then discontinued. On an intent-to-treat analysis, none of the treatments were able to prevent clinical flare-up, but the diet poor in carbohydrates seemed to be effective ($p < 0.05$), although it had the highest number of drop-outs, 20 of 69 (35%).

In a group of patients with CD, we investigated the ability of a new fish oil derivative to modify the phospholipid fatty acid profile in plasma and in red blood cells by means of its fatty acid absorption and incorporation\textsuperscript{25}. This new fish oil formulation had two main characteristics: it was a free fatty acid mixture of 45% EPA and 20% of DHA and was coated in three different manners to minimize the fish oil side effects. The pills were coated with a special gastroresistant coating, to avoid breaking the capsules in the stomach and to obtain the delivery of the n-3 PUFA s to the first part of the small intestine. Our data showed that the free fatty acid mixture seems to be much better absorbed compared with the traditional triacylglycerol mixture and the double mechanism of release enables better absorption and incorporation. We then investigated the possible beneficial effects of this new n-3 PUFA preparation in the maintenance of remission in patients with CD\textsuperscript{26}.

Our patients were in clinical remission for less than 24 months before the study, and all had some laboratory evidence of inflammation. Patients of this type have about a 75% greater risk of relapse compared with patients who are in remission longer and have normal laboratory tests\textsuperscript{27}. 78 patients were enrolled in the one-year study. The patients were randomly assigned to receive either three enteric-coated capsules of fish oil three times daily or three enteric-coated capsules of identical appearance containing 500 mg of placebo three times daily. The placebo contained a mixed acid triglyceride of fractionated fatty acids: 60 percent capryl acid and 40 percent capric acid. The fish oil capsules used contained 500 mg of a new marine lipid concentrate in free fatty acid form (40% EPA and 20% DHA) resulting in daily doses of 1.8 g of EPA and 0.9 g of DHA. The capsules were specially coated to resist gastric acid for at least 30 minutes and to disintegrate within 60 minutes. After 1 year, in the fish oil group (39 patients) 1 patient withdrew (moved away), 4 dropped out because of diarrhoea and 11 relapsed. In the placebo group (39 patients) 1 patient withdrew (moved away), 1 dropped out because of diarrhoea and 27 relapsed (intent-to-treat analysis: relapse rate 41 percent in fish oil group versus 74 percent in placebo group, difference 33 percent, 95 percent confidence interval, 13 to 54, $p = 0.003$). In the five patients with diarrhea, this began within the first month of treatment and did not improve when the daily intake of capsules was reduced. There were no other side effects. A tert one year of treatment 59 percent of the patients in the fish oil group were still in remission, as compared with only 26 percent in the placebo group ($p = 0.006$). Multivariate logistic regression analysis indicated that only fish oil treatment reduced the likelihood of relapse (odds ratio 4.2; 95% confidence interval, 1.6 to 10.7).

As you might probably know, two multicentre, well designed studies – EPIC-1 and EPIC-2 – are ongoing in North America and Europe to test whether a 70 % enteric coated EPA-DHA free fatty acid preparation (Epanova) is efficacious in two subgroup of patients affected by Crohn’s disease. I think these studies will definitely establish if omega-3 fatty acids have a significant effect and can therefore be used for treating inflammatory bowel diseases.
Conclusions

My overall opinion about the majority of trials published so far on n-3 PUFAs for treating IBD patients is that they are not really comparable; n-3 PUFAs were in most cases added to other ongoing treatments such as 5-asa, steroids, immunosuppressors.

The obvious consequence of this overlap of treatments is the impossibility to comment on the real efficacy of n-3 fatty acids per se.

1. In the different studies, diverse kinds of fish oil derivatives preparations (concentrations, chemical form-ethyl-esters, tryglicerides, free fatty-coating) which are characterized by different intestinal absorption and incorporations into tissues (due to many annoying side effects influencing patients’ compliance) were used28-30. As a consequence, the n-3 PUFAs dose assumed daily is not comparable.

2. Although samples are apparently homogeneous two different populations of patients were enrolled, as Crohn’s patients in remission differ depending on the previous remission time they have had. Indeed, a stable remission, which means more than 2 years needs to be distinct from a remission occurring after an acute relapse31. These two subpopulations of Crohn’s disease patients are both in remission but they cannot be compared since their risk of a new flare-up in the 12 following months is significantly different.

3. The placebos used in most of these studies were not real placebo, it is now very well known that olive oil32-35, corn oil etc cannot be considered as such36.

4. Some of these studies were not well designed: the “cross-over design” cannot be used for testing n-3 fatty acids because the “carry over effect” of the omega-3 PUFAs lasts more than 10 weeks (inhibition of cytokine production such as IL-1 beta and TNF alfa)5 and therefore the wash out period (1 month) of these previous studies was not long enough.

I think the bottom line is that the number of well designed available trials is at the moment insufficient to allow any conclusions on the efficacy of omega-3 fatty acids, waiting for the EPIC-1 and EPIC-2 studies.

References


