Omega-3 fatty acids for early rheumatoid arthritis

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The anti-inflammatory effects of high doses of omega-3 fatty acids provide symptomatic relief and also reduce cardiovascular risk in rheumatoid arthritis. Fish oil is a convenient source of these essential fatty acids.

Recent advances in the management of rheumatoid arthritis (RA) include early, intensive use of disease-modifying antirheumatic drugs (DMARDs), with remission as the goal. This goal incorporates avoidance of NSAIDs, which lack disease-modifying effects and confer increased risk for adverse cardiovascular and upper gastrointestinal events.

Fish oil contains natural inhibitors of the pro-inflammatory enzyme cyclooxygenase (COX) and its ingestion in adequate dosages has the beneficial effects of reducing tender joint count in RA, reducing reliance on NSAIDs for RA symptom relief and reducing CV risk. Fish oil therefore warrants consideration as a component of therapy for RA.

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Fish oil and omega-3 fatty acids

Fish oil is rich in long chain omega-3 (n-3) polyunsaturated fatty acids, so-called as the first of the several double bonds is at the n-3 position (i.e. between the third and fourth carbon atoms from the methyl end of the molecule). The predominant omega-3 fatty acids in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); these two usually comprise about 30% (18% EPA and 12% DHA) of the total fatty acids in this oil.

EPA and DHA have anti-inflammatory effects in two ways. They competitively inhibit the COX and 5-lipoxygenase enzymes involved in the metabolism of arachidonic acid (which is the omega-6 analogue of EPA) to proinflammatory and prothrombic omega-6 eicosanoids, and they inhibit inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin-1β (IL-1β). These anti-inflammatory effects are only evident at much higher doses of EPA and DHA than those that begin to reduce cardiovascular risks.

Although various vegetable oils contain omega-3 fats, these are the shorter chain omega-3 fatty acids. The conversion of these into the biologically active long chain omega-3 fatty acids is a relatively inefficient process in humans, partly because of the high levels of omega-6 fatty acids in Western diets. Eating foods fortified with fish oil-derived omega-3 fatty acids, such as some breads, cereals, milks and yoghurts, can contribute to increased daily omega-3 intakes but the amounts of EPA and DHA ingested this way are small compared to eating fish daily. Therefore, the best sources of EPA and DHA are seafood (especially oily fish) and fish oil.

Using fish oil in RA

Fish oil is offered to patients with RA as an adjunctive therapy to DMARDs, which are often used as combinations in maximal tolerated doses in more severe RA. Fish oil and DMARD therapy can be beneficial at any stage in the disease, but it is important to note there is a 'window of opportunity' when effective therapy has the best chance of achieving remission. Both the cardioprotective effects and anti-inflammatory effects of fish oil are important in this early stage of RA as increased cardiovascular risk occurs surprisingly early in the course of the disease.

How is it used?

The 4.5 g of omega-3 fatty acids that is delivered by 15 mL of liquid fish oil is considered to be an effective daily anti-inflammatory dose. Eating enough fish to achieve this dose would not be practicable for most people, hence the use of fish oil. Oil obtained from the body of the fish (excluding the liver) is preferable to cod liver oil, which can deliver undesirable amounts of vitamin A when taken at anti-inflammatory doses.

Encapsulated fish oil is widely used to avoid the fishy taste and odour of the oil. However, as standard fish oil capsules contain only 300 mg EPA plus DHA per 1000 mg capsule, a daily dose of nine standard fish oil capsules is required to provide the minimum anti-inflammatory dose of 2.7 g/day EPA plus DHA. People who self-medicate generally take one or two capsules daily, which is insufficient for an anti-inflammatory effect but may have cardiovascular benefit. Liquid fish oil

Avoiding the taste of fish oil

The fish oil on juice method of ingesting fish oil

- Layer the dose of fish oil over 20 to 30 mL of juice (e.g. orange, tomato, apple, etc) in a small glass – do not stir. Pour a similar amount of juice into another glass.
- With a single gulp, swallow the juice plus fish oil. Avoid the liquid contacting the lips.
- Immediately sip, slowly and through the lips, the juice in the other glass. This will remove any oil from the lips.

Avoiding repeated tasting

Taking the fish oil immediately before a solid meal and without further fluid helps the mixing of the fish oil with food and passage into the small intestine. The oil will otherwise float on free fluid in the stomach and may be partly regurgitated and tasted with venting of swallowed gas. If reflux (repeating taste) becomes a problem, the dose may be split so it is taken before the morning and evening meals.

(Norwegian Omega 18/12 Fish Oil) at a dose of 15 mL/day (equivalent to 14 standard fish oil capsules and thus well into the anti-inflammatory range even for larger people) is a convenient and inexpensive alternative to the capsules. It is important that potential users understand that the symptomatic benefit of fish oil in RA can be delayed two to three months.[1]

Most people find the odour and taste of fish oil unpleasant. A flavouring such as citrus or peppermint can be used to partially mask the taste, or the taste can be avoided by taking the oil by a method that avoids the oil contacting the lips, where it may linger. The box 'Avoiding the taste of fish oil' on this page includes a description of the fish oil on juice method of taking fish oil.[1] The odour of fish oil can be minimised by storing opened bottles of fish oil within their packaging carton and placing them in a refrigerator between doses. Swallowing the fish oil dose quickly and sipping the juice chaser slowly also helps.

Some patients with persistent oesophageal reflux may not be able to take fish oil.

How effective is it?

In RA, there is level 1 evidence for symptomatic improvement with anti-inflammatory doses of fish oil.[1,2] A recent study of patients with early RA who took fish oil for three years demonstrated that patients are prepared to take fish oil in anti-inflammatory doses on a long-term basis with usage rates (about 80%) comparable to typical rates for NSAID use.[3] Conversely, NSAID usage (at about 20%) was reduced substantially. Epidemiological studies show lower frequencies of RA, as well as of cardiovascular disease, in populations that have a higher omega-3 fatty acid-intake through fish,[4] often despite relatively high frequencies of HLA-DR4 alleles (which confer RA disease susceptibility).[5] Although the disease modifying effect of fish oil in RA is unknown, the inhibitory effect of anti-inflammatory doses of fish oil on TNFα and interleukin-1β synthesis suggests a favourable long-term effect on disease progression.[6] Fish oil also has benefits in other autoimmune diseases, reducing relapse rates in Crohn's disease and progression to renal failure in IgA nephropathy,[7] and improving control in systemic lupus erythematosus.

Epidemiological studies and secondary prevention trials after myocardial infarction have shown that dietary fish and fish oil reduce cardiovascular risk. Probably the most potent effect of omega-3 fatty acids is to stabilise the myocardial membrane, thereby reducing ventricular fibrillation and sudden death. A beneficial effect on sudden death was seen with less than 1 g of omega-3 fatty acids per day.[8] Additional cardiovascular benefits can be seen at anti-inflammatory doses, such as reduced blood pressure, reduced fasting triglycerides, more rapid clearance of chylomicrons, increased HDL cholesterol, reduced total cholesterol to HDL cholesterol ratio, reduced atheroma (in experimental animals), improved arterial compliance and flow mediated dilation.[9]

A meta-analysis of large, long-term randomised controlled trials of lipid-lowering agents has shown that increased dietary intake of omega-3 fatty acids reduces mortality by at least as much as the use of statins, the only other intervention to show significant benefit.[10]

How safe is it?

Intolerance to fish oil occurs in about 15% of patients offered the treatment. Unwanted effects of fish oil ingestion include repeating taste, retrosternal burning, diarrhoea and headache. Some patients are unable to accept the idea of taking fish oil because of its odour and taste. In the authors' Early Arthritis Clinic, 15 mL/day of fish oil was not associated with weight gain over one year. There is no evidence of fetal harm with at least moderate doses of fish oil (2.7 g/day of omega-3 fatty acids).

While fish oil has not been associated with any serious acute adverse effects, its long term use raises several theoretical and practical concerns.

Greenland Inuits who ingested 7 g/day omega-3 fatty acids (equivalent to about 24 mL/day fish oil) appeared to have a bleeding tendency that may have contributed to an observed increase in

cerebral haemorrhage. In the context of the Western diet, anti-inflammatory doses of fish oil supplements have not been associated with an increased bleeding tendency, even in patients taking aspirin or warfarin.[11]

Consumption of large carnivorous fish has been associated with increased levels of mercury (as methylmercury) in the blood and urine.[12] Methylmercury is a neurotoxin that impairs neural development in the fetus and infant. Fish oils that have been processed properly contain very little mercury. Increased blood and urine mercury was not seen in the authors' group of patients taking fish oil at a dose of 15 mL/day for more than three years.

Chlorinated biphenyls, which are similar to dioxins, are byproducts of industrial synthesis of organic chemicals. Their effects include carcinogenesis. These compounds are not biodegradable so they accumulate in the marine food chain. They can be removed from fish oils by molecular distillation and should be present at very low levels in most commercial preparations.[13]

Precautions and drug–fish oil interactions

No particular precautions are required in the taking of fish oil. Some of the interactions between fish oil and the various drugs used for arthritis can be useful.[1]

NSAIDs and fish oil

The natural COX inhibitors EPA and DHA in fish oil inhibit both COX-1 and COX-2 activity. The different effects of the omega-3 fatty acids in fish oil and the various NSAIDs on the synthesis of COX-1 and COX-2 products are consistent with the known cardioprotective effect of fish oil and the increased cardiovascular risk associated with NSAIDs (particularly those that are COX-2 selective). NSAIDs tend to cause a moderate increase in systemic blood pressure whereas fish oil reduces blood pressure by a similar amount.[14] Fish oil has not been associated with gastric irritancy.

Methotrexate and fish oil

The dose of methotrexate that can be given is often limited by gastrointestinal toxicity. Omega-3 fatty acids have been shown in animal studies to reduce methotrexate-induced loss of appetite, weight loss and gastrointestinal damage.[16]

Cyclosporin and fish oil

The most common adverse effects of cyclosporin that limit doses are hypertension and impaired renal function. These effects appear to be partially thromboxane-mediated. Fish oil inhibits thromboxane production and, in animal studies, has been shown to reduce both the hypertensive and nephrotoxic effects of cyclosporin.[15]

TNF blockade and fish oil

Although untested in clinical trials, combining fish oil with TNF blockers may be beneficial given the inhibitory effect of anti-inflammatory doses of fish oil in TNFα and IL-1β synthesis.

Conclusion

Fish oil in anti-inflammatory doses is an effective and safe alternative to NSAIDs for symptomatic relief in RA. Fish oil is also effective in reducing cardiovascular risk, which is recognised as the major cause of reduced life expectancy in patients with RA. It also has beneficial effects in other autoimmune diseases. MT

A list of references is available on request to the editorial office

DECLARATION OF INTEREST: Professor Cleland and Dr James have longstanding research interests in the health benefits of dietary omega-3 fats. The Preventive Care Centre of the Royal Adelaide Hospital (RAH) under Professor Cleland's direction distributes fish oil for therapeutic use.
Dr Proudman directs the Early Arthritis Clinic, RAH, in which therapeutic effects of fish oil are under evaluation.
Melrose Laboratories, who market a preparation of bottled fish oil, have donated to the RAH Rheumatology Research Fund.

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