Fish Oil: What the Prescriber Needs to Know

Arthritis Research & Therapy Volume 8, Issue 1, 2006, pp. 402
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FROM ABSTRACT:
There is a general belief among doctors, that patients with arthritis need nonsteroidal anti-inflammatory drugs (NSAIDs). Implicit in this view is that these patients require the symptomatic relief provided by inhibiting synthesis of nociceptive prostaglandin E2, a downstream product of the enzyme cyclo-oxygenase (COX), which is inhibited by NSAIDs.

However, the concept of 'safe' NSAIDs has collapsed following a multiplicity of observations establishing increased risk for cardiovascular events associated with NSAID use, especially but not uniquely with the new COX-2-selective NSAIDs. This mandates greater parsimony in the use of these agents.

Fish oils contain a natural inhibitor of COX, reduce reliance on NSAIDs, and reduce cardiovascular risk through multiple mechanisms. Fish oil thus warrants consideration as a component of therapy for arthritis, especially rheumatoid arthritis, in which its symptomatic benefits are well established.

A major barrier to the therapeutic use of fish oil in inflammatory diseases is ignorance of its mechanism, range of beneficial effects, safety profile, availability of suitable products, effective dose, latency of effects and instructions for administration. This review provides an evidence-based resource for doctors and patients who may choose to prescribe or take fish oil.

Abbreviations

AA	arachidonic acid	COX	cyclo-oxygenase
DHA	docosahexaenoic acid	EPA	eicosapentaenoic acid
LC	long chain	MUFA	monounsaturated fatty acid
NSAID	nonsteroidal anti-inflammatory drug	PBB	polybrominated biphenyl
PCB	chlorinated biphenyl	PG	prostaglandin
PUFA	polyunsaturated fatty acid	RA	rheumatoid arthritis
TNF	tumour necrosis factor	TX	thromboxane

THESE AUTHORS ALSO NOTE:
Omega-6s (n6) and omega-3s (n3) are dietary essential fatty acids which cannot be synthesized endogenously.
Diets in industrialized Western countries are generally abundant in n6 PUFAs and poor in n3 PUFAs.
In addition to fish oils, n3 PUFAs are found in the flesh of all marine fish, including crustaceans and shellfish.
"In fish and fish oils, n3 PUFAs are present as long chain (LC) PUFAs (i.e. 20 and 22 carbon atoms long) PUFAs."
In flaxseed, perilla and to a lesser extent, canola oil, n3 PUFAs are present as the C18 PUFA alpha-linolenic acid (C18:3n3).

"In sunflower, cottonseed, safflower and soy oils, and the spreads manufactured from them, the main fatty acid is the n6 C18 PUFA linoleic acid (C18:2n6). Because Western diets are typically low in LC n3 PUFAs, substantial increases in tissue LC n3 can be achieved by taking a fish oil supplement without further dietary modification. It is unlikely that one can consume the amount of fish required to achieve anti-inflammatory doses of LC n3 PUFAs. The conversion of C18 n3 PUFAs [such as flax oil] to C20 and C22 n3 PUFAs [fish oil] occurs relatively inefficiently in humans, and so vegetable sources of dietary n3 PUFAs alone fail to achieve the tissue levels seen with fish oil."

The pain of arthritis is mediated in part by prostaglandin E2 (PGE2) which is synthesized from the n6 LC PUFA arachidonic acid (AA; 20:4n-6) by the enzyme cyclo-oxygenase (COX).
EPA is both an inhibitor of AA metabolism and an alternate substrate for COX. In addition to its effects on COX metabolism, fish oil in anti-inflammatory doses also inhibits AA metabolism by 5-lipoxygenase [LOX] and thereby reduces production of the potent chemotactic factor leukotriene B4. This effect, attributable to EPA, is not seen with NSAIDs, which have no inhibitory effects on the 5-lipoxygenase pathway.

Other inflammatory mediators inhibited by fish oil are the cytokines tumour necrosis factor alpha (TNF) and interleukin-1 (IL-1), "which are involved not only in production of inflammatory signs and symptoms but also in cartilage degradation." In contrast, TNF-alpha synthesis is increased by NSAIDs.

"The anti-inflammatory dose of fish oil requires delivery of 2.7 g or more of LC n3 PUFAs daily, and that higher doses are also safe and effective. A daily intake of less than 2.7 g EPA plus docosahexaenoic acid (DHA) is "insufficient for an anti-inflammatory effect. The symptomatic benefit of fish oil in RA can be delayed 2–3 months," and "it is important that potential users understand that this delay exists."

Patients should reduce ingestion of n6 PUFA by substituting olive oil for vegetable oils.
At anti-inflammatory doses, cod liver oils, which are rich in the fat-soluble vitamins A and D, contain more vitamin A than recommended intakes. Vitamin A has been associated with reduced bone density and increased risk for hip fracture. Vitamin A toxicity is not a problem with anti-inflammatory doses of fish body oils because they contain very little vitamin A.

The taste of liquid fish oil can be avoided by taking it with juice using a method that avoids contact of fish oil with the lips where the fish oil taste is experienced:
1) Pour 1-2 oz. of juice (e.g. orange, tomato, apple, etc.) into two small 'shot' glasses.
2) "Layer the desired dose of fish oil onto the juice in one glass – do not stir."
3) "Swallow the juice and fish oil with a single gulp, avoiding contact with the lips (where the fish oil can be tasted)."
4) "Immediately sip the juice in the other glass slowly through the lips. This will remove any oil from the lips." If there is any gastric reflux, it is important to reduce the amount of juice chaser.
5) "Take the fish oil immediately before a solid meal and without further fluid. This avoids floating of the oil on fluid in the stomach and favours mixing of the fish oil with food and passage from the stomach into the intestine. If reflux (repeating taste) becomes a problem, then split the dose before morning and evening meals. Alternatively, take the dose then lie on the left side for at least 15 min. In this position the oil floats into the passage from the stomach to the small intestine."

"Fish oil (obtained from the body of the fish) is preferable to cod liver oil, which can deliver undesirable amounts of vitamin A at anti-inflammatory doses. The odour of fish oil can be minimized by keeping fish oil refrigerated once open and taking it quickly once the fish oil on juice technique is mastered."

"Because most anti-inflammatory **drugs** can have adverse effects on the foetus, they are generally withdrawn during pregnancy and lactation."

LC n3 PUFAs are strongly represented among neural lipids, and neural development is particularly active in utero and during infancy.
There is a dramatic fall in maternal plasma DHA in the immediate postpartum period. There is no evidence of harm at supplementation levels of at least 2.7 g/day of LC n-3 PUFAs" during pregnancy.

Fish oils contain the natural COX inhibitor EPA, and therefore fish oil is cardioprotective, reduces blood pressure, reduces pain, and does not have associated gastric irritation. Fish oil has not been associated with any serious acute treatment related syndromes. A dose of 3 g/day EPA plus DHA has been assessed as safe for general consumption.

“Greenland Inuits consuming their aboriginal diet ingest 7 g/day LC n3 PUFAs, and consequently have a very low frequency of myocardial infarction and a low frequency of inflammatory diseases.”

“Within the Western context, fish oil supplements have not been associated with an increased bleeding tendency, even in patients taking aspirin or warfarin for antithrombotic effect.”

“Methylmercury is an industrial contaminant that accumulates in long-lived fish (e.g. swordfish, marlin, sea perch, shark). Methylmercury is a neurotoxin that impairs neural development, especially in the foetus and infants. Fish consumption has been associated with increased blood and urine mercury. Properly processed fish oils contain very little mercury.”

“Chlorinated biphenyls (PCBs) are byproducts of industrial synthesis of organic chemicals. They are structurally related to dioxins and are potentially toxic. PCBs are poorly biodegradable and they accumulate in the land and marine food chains.
Polybrominated biphenyl (PBB) fire retardants are similar to PCBs. Halogenated biphenyls can be removed from fish oils by molecular distillation and should be present at low levels in good quality products.”

“Epidemiological studies show lower frequencies of RA in populations that consume higher amounts of LC n3 fats. Fish oil has therapeutic effects in several inflammatory diseases, including RA, Crohn's disease, progression of renal failure in immunoglobulin A nephropathy, in psoriasis, in systemic lupus erythematosus, and there is strong evidence for cardiovascular benefit.

“Dietary fish and fish oil have been shown to reduce cardiovascular risk in epidemiological studies. The most potent effect of dietary LC n3 PUFAs is to stabilize the myocardial membrane, thereby reducing ventricular fibrillation and sudden death. There is a “striking reduction in cardiac mortality and, in particular, sudden cardiac death seen with fish oil and diets rich in n3 PUFAs. At anti-inflammatory doses of fish oil other cardiovascular benefits can be seen. These include improved blood pressure control, reduced fasting triglycerides, more rapid clearance of chylomicrons, increased high-density lipoprotein cholesterol, reduced total cholesterol to high-density lipoprotein cholesterol ratio, reduced atheroma, and improved arterial compliance.”

Increased LC n3 PUFA intake reduce annualized death rates better than statin drugs. “That fish oil is not used more widely to manage cardiovascular risk appears to reflect more the influence of pharmaceutical product marketing on the practice of ‘evidence-based medicine’ than the merits of fish oil relative to those of commonly used proprietary agents.”

CONCLUSIONS
“In a medical environment in which messages molded by pharmaceutical interests stress the 'need' for NSAIDs, prescribers should consider the NSAID-sparing effects, the lack of serious side effects and the positive health benefits of fish oil. Although modest increases in intake of n3 LC PUFAs can reduce cardiovascular risk, relatively large doses (more than 2.7 g/day EPA plus DHA) are required for anti-inflammatory effects.”

KEY POINTS

1) There is a general belief among doctors that patients with arthritis need nonsteroidal anti-inflammatory drugs (NSAIDs). This is because the pain of arthritis is primarily caused by PGE2, which is derived from the omega-6 fatty acid arachidonic acid through the activity of the enzyme COX. NSAIDs inhibit the COX enzyme.

2) However, NSAIDs increase the risk for cardiovascular events.

3) Fish oils contain a natural inhibitor of COX, reduce reliance on NSAIDs, and reduce cardiovascular risk.

4) Omega-6s (n6) and omega-3s (n3) are dietary essential fatty acids which cannot be synthesized endogenously.

5) Diets in industrialized Western countries are generally abundant in n6 PUFAs and poor in n3 PUFAs.

6) "Because Western diets are typically low in LC n3 PUFAs, substantial increases in tissue LC n3 can be achieved by taking a fish oil supplement."

7) It is unlikely that one can consume the amount of fish required to achieve anti-inflammatory doses (minimum of 2.7 g/day) of LC n3 PUFAs.

8) "The conversion of C18 n3 PUFAs [such as flax oil] to C20 and C22 n3 PUFAs [fish oil] occurs relatively inefficiently in humans, and so vegetable sources of dietary n3 PUFAs alone fail to achieve the tissue levels seen with fish oil."

9) "EPA [fish oil omega-3] is both an inhibitor of AA metabolism and an alternate substrate for COX."

10) "EPA [fish oil omega-3] also inhibits the metabolism of arachidonic acid into leukotriene B4 by LOX enzymes, which NSAIDs do not do. Consequently, EPA fish oil is superior to NSAIDs in creating an anti-inflammatory effect."

11) NSAIDs increase the synthesis of tumor necrosis factor (TNF) alpha which causes both inflammation and cartilage degradation. In contrast, EPA fish oil inhibits TNF alpha.

12) "The anti-inflammatory dose of fish oil requires delivery of 2.7 g or more of LC n3 PUFAs daily." **[Very Important]**

13) A daily intake of less than 2.7 g EPA plus docosahexaenoic acid (DHA) is "insufficient for an anti-inflammatory effect." **[Very Important]**

14) Symptomatic improvement from fish oil supplementation can take 2–3 months, and "it is important that potential users understand that this delay exists."

15) Patients should also reduce ingestion of n6 PUFA by substituting olive oil for vegetable oils.

16) "At anti-inflammatory doses, cod liver oils, which are rich in the fat-soluble vitamins A and D, contain more vitamin A than recommended intakes." Vitamin A has been associated with reduced bone density and increased risk for hip fracture.

17) Vitamin A toxicity is not a problem with anti-inflammatory doses of fish body oils because they contain very little vitamin A. **[Important]**

18) “Fish oil (obtained from the body of the fish) is preferable to cod liver oil, which can deliver undesirable amounts of vitamin A at anti-inflammatory doses.”

19) “The odour of fish oil can be minimized by keeping fish oil refrigerated once open.”

20) “Because most anti-inflammatory **drugs** can have adverse effects on the fetus, they are generally withdrawn during pregnancy and lactation.”

21) LC n3 PUFAs are strongly represented among neural lipids, and neural development is particularly active in utero and during infancy.

22) “There is a dramatic fall in maternal plasma DHA in the immediate postpartum period.”

23) “There is no evidence of harm at supplementation levels of at least 2.7 g/day of LC n-3 PUFAs” during pregnancy.

24) “Within the Western context, fish oil supplements have not been associated with an increased bleeding tendency, even in patients taking aspirin or warfarin for antithrombotic effect.”

25) “Methylmercury is an industrial contaminant that accumulates in long-lived fish (e.g. swordfish, marlin, sea perch, shark).”

26) “Methylmercury is a neurotoxin that impairs neural development, especially in the foetus and infants.”

27) Fish consumption is associated with increased blood and urine mercury.

28) “Properly processed fish oils contain very little mercury.”

29) “Chlorinated biphenyls (PCBs) are byproducts of industrial synthesis of organic chemicals. They are structurally related to dioxins and are potentially toxic.”

30) PCBs are poorly biodegradable and they accumulate in the land and marine food chains.

31) Polybrominated biphenyl (PBB) fire retardants are similar to PCBs.

32) “Halogenated biphenyls can be removed from fish oils by molecular distillation and should be present at low levels in good quality products.”

33) There is a “striking reduction in cardiac mortality and, in particular, sudden cardiac death seen with fish oil and diets rich in n3 PUFAs.”

34) Increased LC n3 PUFA intake reduce annualized death rates better than statin drugs. “That fish oil is not used more widely to manage cardiovascular risk appears to reflect more the influence of pharmaceutical product marketing on the practice of ‘evidence-based medicine’ than the merits of fish oil relative to those of commonly used proprietary agents.”

35) “In a medical environment in which messages molded by pharmaceutical interests stress the 'need' for NSAIDs, prescribers should consider the NSAID-sparing effects, the lack of serious side effects and the positive health benefits of fish oil.”

36) “Although modest increases in intake of n3 LC PUFAs can reduce cardiovascular risk, relatively large doses (more than 2.7 g/day EPA plus DHA) are required for anti-inflammatory effects.”