Review

Fish oil: what the prescriber needs to know

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Abstract

There is a general belief among doctors, in part grounded in experience, 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 E_2, 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.

Introduction

Essential dietary constituents are those that cannot be synthesized endogenously. Vitamins are familiar examples of essential micronutrients. The dietary essential fatty acids are polyunsaturated fatty acids (PUFAs) that contain the n6 with or without the n3 double bond, neither of which can be synthesized endogenously. The n6 (or ω6) PUFAs contain the n6 double bond, and the n3 (or ω3) PUFAs have both n6 and n3 double bonds. (The n or ω notation refers to the position of the double bond relative to the methyl terminus of the fatty acid molecule.) In contrast to vitamins, n6 and n3 fatty acids are macronutrients, and diets in industrialized Western countries are generally abundant in n6 PUFAs and poor in n3 PUFAs. This is potentially important because the ratios of these fatty acids in the tissues are determined largely by their ratios in the diet [1,2].

Dietary sources of n3 and n6 polyunsaturated fatty acids

In seeking to alter the balance of n3 and n6 PUFAs in the tissues with therapeutic intent, it is necessary to understand which foods are rich in these fatty acids. This allows n3-rich items to be selected and n6-rich items to be avoided. 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 [C20 and C22, respectively]) PUFAs. In certain vegetable oils, notably flaxseed, perilla and, to a lesser extent, canola oil, n3 PUFAs are present as the C18 PUFA α-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). Olive oil and canola oil are rich sources of oleic acid (C18:1n9), which is a monounsaturated fatty acid (MUFA) containing a single double bond in the n9 position. Oleic acid can be endogenously synthesized by humans, and so it is not an essential fatty acid (Table 1).

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 [3]. However, choice of spreads that are rich in n3 PUFAs or rich in MUFAs and low in n6 PUFAs allows higher tissue n3 levels to be reached with a given dose of fish oil [3,4]. To achieve anti-inflammatory doses of LC n3 PUFAs by eating fish, a more substantial intake is required than would be practical for most people. The conversion of C18 n3 PUFAs to C20 and C22 n3 PUFAs occurs relatively inefficiently in

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.

Table 1

Dietary sources of fatty acids

Foods and ingredients	Fatty acids contained in the foods	Comments
Fish and/or fish oil	Long chain n3 PUFAs such as EPA (C20:5n-3) and DHA (C22:6n-3)	EPA and DHA are the beneficial n3 PUFAs
Flaxseed and canola oil	The shorter chain n3 PUFA ALA (C18:3n-3).	ALA is converted to EPA or DHA after ingestion, but not very efficiently. However, it can still provide a useful dietary source of EPA and DHA precursor. Whether it has a direct beneficial effect is unknown
Olive and canola oil	The MUFA OA (C18:1n-9)	OA has a neutral effect on n-3 PUFA metabolism and incorporation into tissues; therefore, it provides a useful 'background' dietary fat for maximizing n3 tissue content from dietary n3 PUFAs
Sunflower, peanut, soybean and cottonseed oil	The n6 PUFA LA (C18:2n-6)	Intake in modern Western diets is generally high and far in excess of what is required to prevent deficiency. Dietary LA can decrease conversion of dietary ALA to tissue EPA and can decrease tissue levels of EPA and DHA. LA is a precursor of AA (C20:4n-6), which is a metabolic antagonist of EPA

AA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MUFA, monounsaturated fatty acid; OA, oleic acid; PUFA, polyunsaturated fatty acid.

humans, and so vegetable sources of dietary n3 PUFAs alone fail to achieve the tissue levels seen with fish oil [5].

Biochemical rationale

Eicosanoids: cyclo-oxygenase pathway

The pain of arthritis is mediated in part by prostaglandin (PG)E_2 – a nociceptive factor that is synthesized at sites of inflammation through the inducible isoform of cyclo-oxygenase (COX), namely COX-2. The COX isozymes, whether COX-1 or COX-2, are inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs).

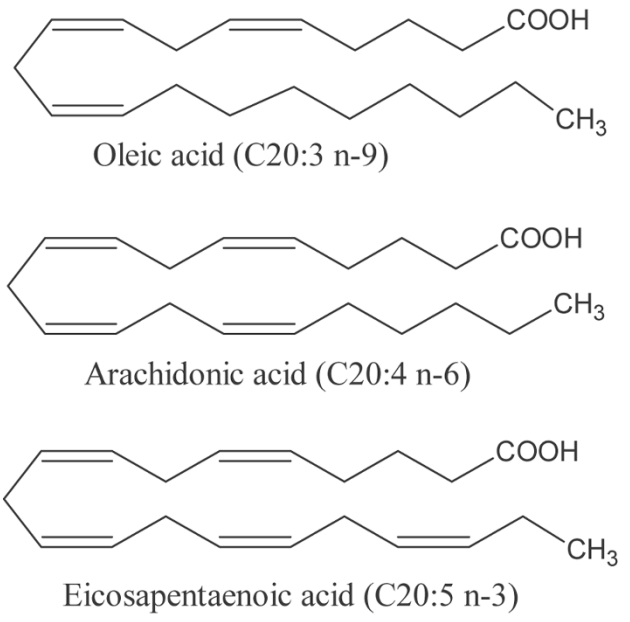
The usual substrate for the COX isozymes is the n6 LC PUFA arachidonic acid (AA; 20:4n-6). Eicosapentaenoic acid (EPA; 20:5n-3), which is present in fish oil, differs from AA only by the presence of its n3 bond (Fig. 1).

Being a chemical homologue, EPA is both an inhibitor of AA metabolism and an alternate substrate for COX. Whereas AA is converted by COX to the n6 prostaglandin PGH_2, EPA is converted to the n3 homologue PGH_3. The latter influences the synthesis of downstream products of COX in ways not seen with NSAIDs (Fig. 2). PGH_3 is an inhibitor but a poor substrate of PGE synthase. PGH_3 is both inhibitor and alternate substrate of thromboxane (TX) synthase but the n3 product TXA_3 has little biological activity. PGH_3 is a poor inhibitor of PGI synthase and is converted to PGI_3, which has activity similar to that of PGH_2. Thus, the net effect of fish oil is to reduce the production of proinflammatory and anti-thrombotic eicosanoids (PGE_2 and TXA_2, respectively) but not the vascular patency factor prostacyclin (PGI_2; Fig. 2) [6].

The effect on PGE_2 may explain in part the symptomatic benefit of fish oil seen in rheumatoid arthritis (RA) [7,8] (see the section on clinical evidence for the anti-inflammatory effects of fish oil, below) and the reduced discretionary use of NSAIDs seen in RA patients taking anti-inflammatory doses of fish oil [9-11].

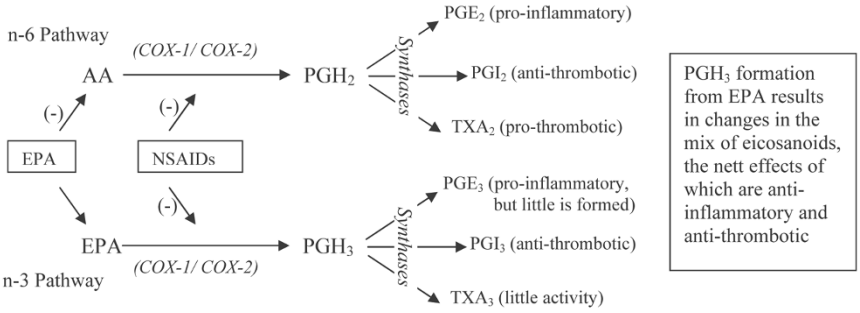
The development of selective COX-2 inhibitors for use as NSAIDs with reduced or no upper gastrointestinal adverse effects was predicated on the observation that PGE_2 at inflammatory foci was COX-2 derived, whereas gastro-protective PGE_2 was COX-1 derived. This scheme fails to

Figure 1



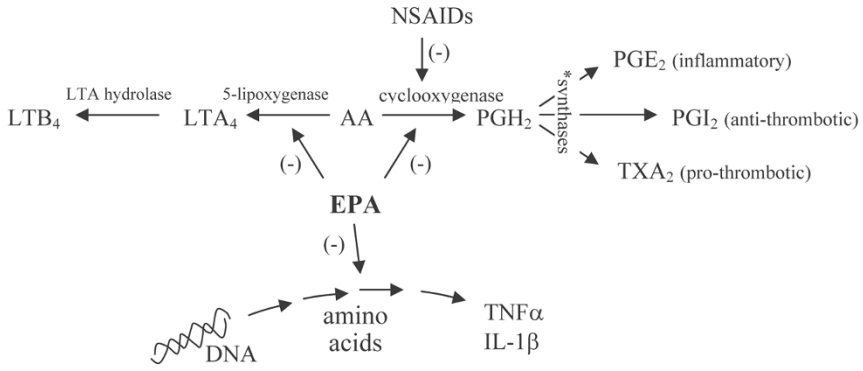
20-Carbon fatty acid homologues.

Figure 2



Metabolism of AA or EPA by COX. –, inhibition; AA, arachidonic acid; COX, cyclo-oxygenase; EPA, eicosapentaenoic acid; NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin; TX, thromboxane.

Figure 3



Effect of EPA on the production of eicosanoids and inflammatory cytokines. *Three different synthases (PGE, PGI, and TX synthase), each with different enzyme kinetic characteristics. –, inhibition; AA, arachidonic acid; COX, cyclo-oxygenase; EPA, eicosapentaenoic acid; IL, interleukin; LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin; TNF, tumour necrosis factor; TX, thromboxane.

acknowledge that PGH_2 and not PGE_2 is the immediate product of AA metabolism by COX, and that PGH_2 is the common precursor for many eicosanoids, including vaso-active and platelet active TXA_2 and prostacyclin (PGI_2; Fig. 2). For reasons explained by the enzymology of the individual synthases, antithrombotic PGI_2 is mainly COX-2 derived whereas prothrombotic TXA_2 is mainly COX-1 derived [12]. Thus, selective COX-2 inhibitors suppress prostacyclin synthesis but not thromboxane synthesis [13,14], which is a potential mechanism for the excess of adverse cardiovascular events seen with use of the coxibs [15]. This outcome is not observed with use of dietary EPA as fish oil.

Eicosanoids: 5-lipoxygenase pathway

In addition to its effects on COX metabolism, fish oil in anti-inflammatory doses also inhibits AA metabolism by 5-lipoxygenase and thereby reduces production of the potent chemotactic factor leukotriene B_4 (Fig. 3) [16,17]. This effect, attributable to EPA, is not seen with NSAIDs, which have no inhibitory effect on the 5-lipoxygenase pathway.

Cytokines

Other inflammatory mediators whose production is inhibited by fish oil are the cytokines tumour necrosis factor (TNF)-α and interleukin-1β, which are involved not only in production of inflammatory signs and symptoms but also in cartilage degradation (Fig. 3) [18-21]. In contrast to its inhibition by fish oil, TNF-α synthesis by monocytes is increased by NSAIDs [22].

Clinical evidence for the anti-inflammatory effects of fish oil

Fish oil has been shown to reduce symptoms in RA in a dose-dependent manner [8,23], relapse rates in Crohn's disease [24] and progression to renal failure in immunoglobulin A nephropathy [25]. Fish oil improves control in systemic lupus erythematosus [26] and has a preventive effect when given prophylactically to mice genetically predisposed to lupus [27].

Dose–response relationships

Investigations across a variety of inflammatory diseases have used doses of fish oil that provide daily intakes of LC n3

Table 2

Fatty acid information for food choices

Foods, ingredients	Choices	Fatty acids
Cooking oils, salad dressings and spreads	Choose:	
	Canola oil products	ALA (18-carbon n3 PUFA)
	Olive oil products	OA (MUFA)
	Avoid:	
	Sunflower, cottonseed, peanut, soybean oil products	LA (18-carbon n-6 PUFA)
Preprepared food such as frozen chips/fries	Nutrient information on the packet will allow a choice of foods prepared in canola or olive oils	
Fish	Because fish oil is rich in long chain n3 fats, fatty fish (e.g. sardines, herrings) have higher n3 content than lean fish. However, all marine fish contain long chain n3 fats. Canned fish have n3 fat content also, but note that canned tuna has less fat (and therefore less n3 fat) than fresh tuna	EPA (20-carbon n3 PUFA) DHA (22-carbon n-3 PUFA)
Nuts and seeds	Flaxseed (linseed)	High in n3 PUFAs
	Walnuts	Some n3 PUFAs but also n6 PUFAs
	Macadamia, almonds	High in MUFA, low in n6 PUFAs
	Peanuts, cashews, brazil and hazel nuts	Some MUFA, but also n6 PUFAs

ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MUFA, monounsaturated fatty acid; OA, oleic acid; PUFA, polyunsaturated fatty acid.

PUFAs that range from less than 1 g to more than 6 g [8]. Collectively, these studies indicate that 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 2.7 g EPA plus docosahexaenoic acid (DHA) is provided by a daily dose of nine or more standard fish oil capsules, which typically contain 30% LC n3 PUFAs w/w. People who self medicate with fish oil generally take one or two capsules daily. This is insufficient for an anti-inflammatory effect but it may provide cardiovascular benefit.

Delay of symptomatic benefits

The symptomatic benefit of fish oil in RA can be delayed 2–3 months [8]. Earlier improvement with higher doses suggests a possible loading effect. It is important that potential users understand that this delay exists.

Influence of background diet

Increased ingestion of n3 PUFAs from vegetable sources yields modest changes in LC n3 PUFAs in most tissues compared with fish oils taken in anti-inflammatory doses. However, avoidance of n6 PUFAs in visible fats (i.e. spreads, cooking oils, mayonnaise, nuts) can increase LC n3 PUFA levels achieved with a given dose of fish oil [3]. Reduction in n6 PUFA intake can be achieved simply by choosing options that are rich in MUFAs, such as olive oil or canola oil based products, or that are rich in n3 PUFAs, such as flaxseed oil or fresh ground flaxseed. Patients should be advised to avoid products labelled as containing polyunsaturated oils because this generally means an n6-rich oil. Canola and olive oil based products generally are so marked. The substitutes suggested above are inexpensive and contain little undesirable saturated fat. A suggested guide to background diet is given in Table 2.

Cost

Cost has been a major impediment to use of fish oil in anti-inflammatory doses. At the time of the major trials of fish oil in RA in the 1980s and 1990s, the cost for 1 g fish oil capsules was typically 30 c per capsule. For 15 capsules of fish oil daily (an average dose for RA trials showing benefit), the annual cost at this price is about A$1650 per annum. For most users this cost is prohibitive, and is particularly discouraging when most other treatments are government subsidized. The Pharmaceutical Benefits Scheme in Australia makes subsidized drugs, irrespective of actual cost, available to consumers at A$4.60 for Health Cardholders and A$28.60 for others for a typical 1-month supply. Fish oil, although available without prescription and with unrestricted access, is thus far more expensive to users than even highly expensive subsidized drugs. Recently, the cost of fish oil capsules has fallen. Products are now available that provide large numbers of capsules at an average cost as low as 10 c per capsule. Although this has reduced the annual cost for an anti-inflammatory dose to about A$550, the cost remains almost twice what non-Health Cardholders pay for most pharmaceutical products. The cost can be reduced substantially by using bottled fish oil taken on juice, a 15 ml daily dose of which costs about A$150 per annum. This

makes fish oil somewhat less expensive than many standard medications for non-Health Cardholders but more expensive than the approximately A$55 per annum paid by Health Cardholders per medication below the safety net.

Availability and merits of different fish oils

Oils derived from marine fish oil all contain LC n3 PUFAs. Standard fish oil is extracted from fish bodies and typically contains EPA 18% and DHA 12% w/w. Until recently, this was available only in capsules, but now a bottled preparation is available in Australia. Cod liver oil is widely available as both bottled oil and in capsules. It contains approximately 10% EPA and 10% DHA, and so it is also a good source of LC n3 PUFAs. However, 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. Although the amount does not cause symptoms of toxicity, similar doses have been associated with reduced bone density and increased risk for hip fracture in epidemiological studies [28]. This is not a problem with fish body oils, which contain very little of these fat-soluble vitamins.

Technique for taking bottled fish oil

Fish oil has a taste and odour that most people find unpleasant, and for this reason it has been largely distributed within capsules. However, the taste of fish oil can be masked partially with flavouring (e.g. citrus, peppermint). The taste can be avoided more completely by taking fish oil on juice using a method that avoids contact of fish oil with the lips where the fish oil taste is experienced.

1. Pour 30–50 ml 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.
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.
6. 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.

Avoidance of 'repeating' taste

The repeating taste of fish oil arises from its low specific gravity, which is less than that of water. Thus, fish oil will float on free fluid with the stomach, in the same way that it floats on juice within a glass. Thus, when an eructation occurs to vent the stomach of swallowed gas, fish oil at the gas–fluid interface in the stomach may be partly regurgitated and tasted. This experience can be minimized by avoiding unnecessary fluids at the time of ingestion of fish oil, avoiding aerated drinks and by taking fish oil immediately before a meal. The latter strategy allows fish oil to mix with food, with which it exits from the stomach into the small bowel. These measures are generally effective in avoiding a 'repeating' fish oil taste. In cases where a problem still exists, passage of fish oil into the duodenum can be facilitated by lying in the left lateral decubitus position; this allows the oil to float into the duodenum, which is above the stomach in this position [29]. Some may have a lesser problem with capsules than fish oil on juice but these can also be problematic because fish oil is released from capsules within the stomach. Some patients with persistent oesophageal reflux may not be able to take fish oil.

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.

Effect of fish oil on body weight

Fish oil, like any fat, is rich in calories. However, most people eat to satiety. In our Early Arthritis Clinic, a cohort of 33 RA patients taking fish oil at the rate of 15 ml/day immediately before or during a meal did not increase their mean weight over 1 year; there was a nonsignificant mean change of −0.4 kg from baseline to 1 year. Metabolic studies suggest the LC n3 PUFAs present in fish oil can reduce adipocyte numbers and the contribution of adipose tissue to body mass [30].

Use in pregnancy

Because most anti-inflammatory drugs can have adverse effects on the foetus, they are generally withdrawn during pregnancy and lactation. Early observations in patients with active RA suggest a tendency toward lessening disease activity in pregnancy. This improvement presumably results from release of immunosuppressive factors that are generated during pregnancy, putatively to prevent immunological rejection of the foetus. In the modern era, in which RA is generally well suppressed by medications, withdrawal of medication in anticipation of and during pregnancy often results in increased disease activity. It is therefore appropriate to consider the safety of fish oil in pregnancy, either as an alternative or as one component of established treatment that may be continued.

LC n3 PUFAs are strongly represented among neural lipids. Neural tissue forms a disproportionately high proportion of body weight in foetuses and, relative to adults, neural development is particularly active *in utero* and during infancy. n3 PUFAs provided through placental transfer to the foetus or in breast milk, which is rich in LC n3 PUFAs, supports requirements for this development. As a result the possibility of depletion of maternal LC n3 PUFA stores exists. There is a dramatic fall in maternal plasma DHA in the immediate postpartum period, which is a time when relapse or onset of

RA is more frequent, especially in women who breast feed [31,32]. Although there are no studies comparing women receiving fish oil with control women, hypothetically n3 depletion could play a role.

Populations with high maternal n3 intakes have higher infant birth weight [33]. In premature infants, breast feeding and n3-enriched infant formula have been associated with accelerated neural development compared with their counterparts given n3 PUFA poor formula [34]. Although there are no studies into the anti-inflammatory effects of fish oil in pregnancy, symptomatic benefit in RA studies, in which women typically outnumber men, is well established. Thus, there is a rationale for use of fish oil in pregnant and lactating women with RA, and there is no evidence of harm at supplementation levels of at least 2.7 g/day of LC n-3 PUFAs [32]. This dose is provided by 10 ml bottled fish oil (not cod liver oil) or the equivalent 9 or 10 standard fish capsules per day, and is in the range of doses shown to have anti-inflammatory effect. There is no evidence higher doses would be toxic to mother or foetus, but a conservative approach would be to limit the fish oil dose to this level. In pregnancy oesophageal reflux is common. Accordingly, attention to time of dosing (preferably morning or middle of the day and immediately before or during the early phase of a low fat meal) and reduced amount of juice with the dose and its chaser may be especially important.

Drug–fish oil interactions

There are several potentially useful drug–fish oil interactions relevant to the management of arthritis.

Fish oil and nonsteroidal anti-inflammatory drugs

As discussed under biochemical rationale (see above), fish oils contain the natural COX inhibitor EPA, which inhibits both COX-1 and COX-2 activity. The different effects of EPA and NSAIDs on synthesis of downstream products are consistent with the known cardioprotective effect of fish oil and increased cardiovascular risk associated with NSAIDs (especially those that are COX-2 selective). Fish oils have been shown to reduce discretionary NSAID use for analgesia by about 50%. Fish oil has not been associated with gastric irritancy. NSAIDs tend to cause a moderate increase in systemic blood pressure, whereas fish oil reduces blood pressure by a similar amount [35,36].

Fish oil and cyclosporin

The most common dose-limiting effects of cyclosporin are hypertension and impaired renal function. These effects appear to be in part thromboxane mediated [37]. Fish oil inhibits TXA_2 production and reduces both the hypertensive and nephrotoxic effects of cyclosporin [38].

Fish oil and tumour necrosis factor blockade

Fish oil in anti-inflammatory doses inhibits TNF and interleukin-1 synthesis by peripheral blood mononuclear cells stimulated *ex vivo* [18,20,21]. A rationale therefore exists for concomitant use of fish oil and TNF blockers. To date, this combination has not been evaluated in formal clinical trials.

Fish oil and methotrexate

Gastrointestinal toxicity is common with methotrexate therapy and is often dose limiting. Animal studies show that LC n3 PUFAs reduce loss of appetite, weight loss and gastrointestinal damage associated with methotrexate therapy [39].

Intolerance to fish oil

Intolerance to fish oil is not unusual and occurs in about 15% of patients offered this treatment. Unwanted effects include repeating taste, retrosternal burning, diarrhoea, aversion to odour and taste, headache and failure to mask taste. Some patients are unable to accept the idea of taking fish oil. Serious unwanted effects have not been reported.

Continuation rates

In a long-term study of fish oil in RA (>3 years), the continuation rate for fish oil was about 80% (unpublished data). This compared favourably with the continuation rates for each of the first-line disease-modifying antirheumatic drugs used concurrently, namely methotrexate, sulphasalazine and hydroxychloroquine.

Safety

Although fish oil has not been associated with any serious acute treatment related syndromes, its long-term use raises several theoretical and practical concerns. These are discussed below.

Safe limits of long chain n3 polyunsaturated fatty acid ingestion

A dose of 3 g/day EPA plus DHA has been assessed as safe for general consumption [40]. Greenland Inuits consuming their aboriginal diet of sea mammals, sea birds and fish ingest 7 g/day LC n3 PUFAs [41]. These Inuits appear to have a bleeding tendency, which may contribute to an observed increase in apoplexy (cerebral haemorrhage) [42]. The very high consumption of LC n3 PUFAs in this population occurs within the context of a low n6 PUFA intake. The equivalence of AA and EPA in Inuit platelet cell membranes (AA:EPA ratio 1:1) was not reached closely by Australian patients taking 4.5 g fish oil for RA (AA:EPA ratio 4:1) for more than 3 years, although this ratio is substantially different from that in healthy Australian control individuals not taking fish oil and consuming an ordinary diet (AA:EPA ratio 40:1) [19,43]. The Inuits have a very low frequency of myocardial infarction (relative risk 0.075 compared with Danish control individuals), which appears to be due in major part to dietary PUFAs [42]. They also have a low frequency of inflammatory diseases. For patients with a chronic inflammatory disease such as RA, which is associated with high cardiovascular risk [44], the reduced cardiovascular risk with and anti-inflammatory effect of fish oil is likely to yield an overall long-term advantage. The

disease-modifying effect of fish oil in RA, positive or negative, is unknown. However, the inhibitory effect of anti-inflammatory doses of fish oil on TNF and interleukin-1 synthesis provides the potential basis for a favourable long-term effect on disease progression.

Bleeding tendency

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 [45].

Lipid peroxidation

Concerns have been raised that fish oils, which contain highly unsaturated n3 PUFAs, lead to accumulation of lipid peroxides in vessels, which may increase cardiovascular risk. There is no convincing evidence that such a pathological accumulation is aggravated by fish oil. In any case, the overall effect of fish oil is to reduce rather than increase cardiovascular risk [46].

Mercury

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 [47,48]. Properly processed fish oils contain very little mercury. Increased blood and urine mercury was not seen in a group of patients taking fish oil at 15 ml/day (4.5 g EPA plus DHA per day) for more than 3 years (unpublished data).

Halogenated biphenyls

Chlorinated biphenyls (PCBs) are byproducts of industrial synthesis of organic chemicals. They are structurally related to dioxins and are potentially toxic. Industrial processes that produce PCBs have been outlawed because these compounds are poorly biodegradable and they have been found to accumulate in the land and marine food chains. Of continuing concern are polybrominated biphenyl (PBB) fire retardants, the production of which is still allowed. With regard to their poor biodegradability, accumulation and toxic potential, PBBs are similar to PCBs. Although the level of environmental contamination of PBBs is substantially less than that of PCB, their continued production means increasing accumulation, and alternatives are being sought. Halogenated biphenyls can be removed from fish oils by molecular distillation and should be present at low levels in good quality products [49].

Possible preventive effects against inflammatory disease

Epidemiological studies show lower frequencies of RA in populations that consume higher amounts of LC n3 fats [50]. However, these differences could be due to incidental unidentified environmental or genetic factors. With regard to the latter, the RA disease susceptibility epitope is not responsible because the Japanese and Inuits, who have high fish intakes and low prevalence of RA, both have relatively high frequencies of DR4 alleles, which confer disease susceptibility [51,52].

Control of disease activity in systemic lupus erythematosus can be improved with fish oil, as shown in clinical studies and in murine lupus. In the latter, preventive regimens, begun at an age before the disease emerges, can have a strong preventive effect [27]. Considering the safety of fish oil and the increased cardiovascular risk seen in lupus, fish oil seems a reasonable option for treatment of 'minimal lupus', which is defined as the presence of arthralgia and a strongly positive antinuclear antibody. (Fish oil might reasonably be combined with hydroxychloroquine in this setting, and has the advantage of freedom from serious unwanted effects.)

Range of therapeutic applications of fish oil

As discussed under clinical evidence for the anti-inflammatory effects of fish oil (see above), fish oil has been found to have therapeutic effects in several inflammatory diseases. Fish oil has been studied most intensively in RA, where there is level 1 evidence for symptomatic improvement [8]. There is level 2 evidence for a strong preventive effect against relapse in Crohn's disease and against progression of renal failure in immunoglobulin A nephropathy [24,25]. Some types of psoriasis (guttate, pustular) have been shown to improve with oral fish oil given in anti-inflammatory doses [53-55]. Fish oil improves control in systemic lupus erythematosus [26,56]. In addition to this catalogue of disorders, which share an autoimmune-based inflammation in their pathogenesis, there is strong evidence for cardiovascular benefit with fish oil.

Cardiovascular benefit

Dietary fish and fish oil have been shown to reduce cardiovascular risk in epidemiological studies and in secondary prevention trials after myocardial infarction. Perhaps the most potent effect of dietary LC n3 PUFAs is to stabilize the myocardial membrane, thereby reducing ventricular fibrillation and sudden death.

The antiarrhythmic effect of LC n3 PUFAs has been demonstrated *in vitro* in studies of cardiomyocytes challenged by various stimuli [57]. Fish oil or purified n3 fatty acids reduced the incidence of arrhythmias in animal models of ischaemically induced ventricular fibrillation [58,59]. These findings correlate with the striking reduction in cardiac mortality and, in particular, sudden cardiac death seen with fish oil and diets rich in n3 PUFAs from vegetable sources after myocardial infarction [46,60,61]. This effect on sudden death can be seen with under 1 g/day LC n3 PUFAs (i.e. less than the anti-inflammatory dose) [46].

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 (in experimental animals), and improved arterial compliance and flow mediated dilation (for review, see Din and coworkers [62]).

Importantly, a meta-analysis of large, long-term randomized controlled trials of anti-lipidaemia agents [63] showed that strategies that increase LC n3 PUFA intake reduce annualized death rates to an extent as least as great as that with statins, which is the only other intervention to have significant benefit. 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.

Conclusion

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. Importantly, recipients should be informed that there is a 'mainstream' evidence base for such a recommendation, thereby distinguishing dietary n3 fats from many other nonprescription items that are grouped loosely as 'complementary medicines'.

Although modest increases in intake of n3 LC PUFAs can reduce cardiovascular risk, relatively large doses (≥2.7 g/day EPA plus DHA) are required for anti-inflammatory effects. These doses can be taken efficiently and economically as liquid fish oil on juice. Recipients should be informed that there are multiple strategies for increasing n3 intake, and therefore, no matter what are their usual dietary preferences, there should be an acceptable approach for most individuals.

Competing interests

The authors declare the following complementary interests. LGC and MJJ in particular have longstanding research interests in the health benefits of dietary ω3 fats. The Preventive Care Centre of the Royal Adelaide Hospital, under LGCs' direction, distributes fish oil for therapeutic use. SMP directs the Early Arthritis Clinic of the Royal Adelaide Hospital, in which therapeutic effects of fish oil are under evaluation.

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