

The Role of Fish Oils in the Treatment of Rheumatoid Arthritis

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Abstract

Fish oils are a rich source of omega-3 long chain polyunsaturated fatty acids (n-3 LC PUFA). The specific fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are homologues of the n-6 fatty acid, arachidonic acid (AA). This chemistry provides for antagonism by n-3 LC PUFA of AA metabolism to pro-inflammatory and pro-thrombotic n-6 eicosanoids, as well as production of less active n-3 eicosanoids. In addition, n-3 LC PUFA can suppress production of pro-inflammatory cytokines and cartilage degradative enzymes.

In accordance with the biochemical effects, beneficial anti-inflammatory effects of dietary fish oils have been demonstrated in randomised, double-blind, placebo-controlled trials in rheumatoid arthritis (RA). Also, fish oils have protective clinical effects in occlusive cardiovascular disease, for which patients with RA are at increased risk.

Implementation of the clinical use of anti-inflammatory fish oil doses has been poor. Since fish oils do not provide industry with the opportunities for substantial profit associated with patented prescription items, they have not received the marketing inputs that underpin the adoption of usual pharmacotherapies. Accordingly, many prescribers remain ignorant of their biochemistry, therapeutic effects, formulations, principles of application and complementary dietary modifications. Evidence is presented that increased uptake of this approach can be achieved using bulk fish oils. This approach has been used with good compliance in RA patients. In addition, an index of n-3 nutrition can be used to provide helpful feedback messages to patients and to monitor the attainment of target levels.

Collectively, these issues highlight the challenges in advancing the use of fish oil amid the complexities of modern management of RA, with its emphasis on combination chemotherapy applied early.

Dietary fish oil supplementation has been shown to reduce symptoms in chronic rheumatoid arthritis (RA). In spite of substantial data from clinical trials, a compelling mechanistic rationale and absence of serious unwanted effects, the application of fish oil treatment in RA is not applied universally and ignorance prevails regarding important aspects of mode of action and practical implementation.

1. Mechanisms of Action

Fish oil contains two biologically important omega-3 long chain polyunsaturated fatty acids (n-3 LC PUFA), eicosapentaenoic acid (20:5 n-3; EPA) and docosahexaenoic acid (22:6 n-3; DHA). Both fatty acids, and EPA in particular, have close homology with arachidonic acid (20:4 n-6; AA), with EPA and AA differing only in the presence or absence of the

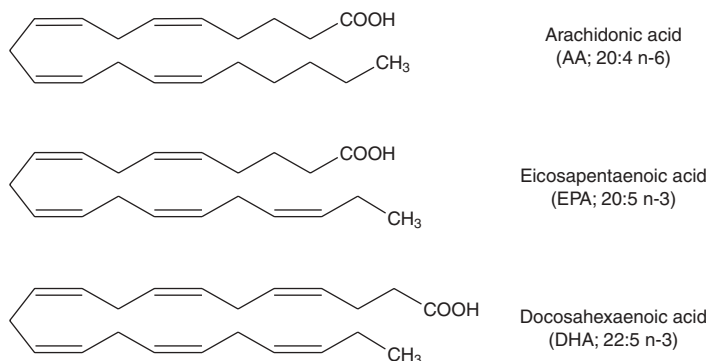


Fig. 1. Structures of long-chain omega-6 and omega-3 fatty acids.

omega-3 (n-3) double bond respectively (figure 1). Both EPA and DHA are competitor substrates that inhibit oxidation of AA by the cyclooxygenase (COX) and lipoxygenase enzymes that are pivotal in the production of the C20 oxylipids, known as eicosanoids (eicosa means twenty in Greek) [figure 2]. These mediators are important in regulating various homeostatic functions, including the gastric mucosal integrity, vascular patency, haemostasis and inflammation.

EPA is converted to an array of products that differ from their n-6 (AA-derived) counterparts in the presence of the n-3 double bond. Since the subscript designation of eicosanoids, e.g. AA derived prostaglandin (PG)-E₂, refers to the number of double bonds present, the EPA derived eicosanoids have a subscript designation that is one integer higher (e.g. PGE₃) than those derived from AA. The presence of the additional n-3 double bond can have an important effect on biological activity, as is the case with EPA-derived leukotriene B₅ (LTB₅),

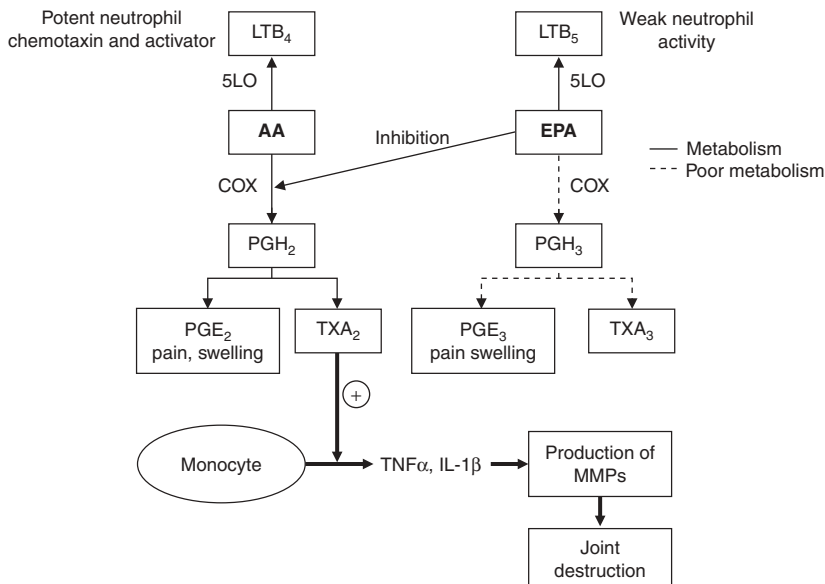


Fig. 2. Metabolism of omega-6 and omega-3 20-carbon fatty acids. 5LO = 5-lipoxygenase; AA = arachidonic acid; COX = cyclooxygenase-1 or -2; EPA = eicosapentaenoic acid; IL = interleukin; LTB = leukotriene B; MMP = matrix metalloproteinase; PGE = prostaglandin E; PGH = prostaglandin H; TNF = tumour necrosis factor; TXA = thromboxane.

which has little of the chemotactic or stimulatory effect on leucocytes of LTB₄.^[1] Similarly, thromboxane (TX)-A₃ has little of the activity of TXA₂ as a vasoconstrictor and stimulus for platelet aggregation.^[2] The relative lack of agonist effect of TXA₃ seen in the vascular system seems likely to extend to the up-regulatory effect of TXA on tumour necrosis factor (TNF)- α and interleukin (IL)-1 β synthesis by monocytes, since this effect is also TX receptor mediated.^[3] The observed inhibitory effect of fish oil supplementation on TXA₂ synthesis may thus explain its inhibitory effect on TNF α and IL-1 β synthesis.^[4] This effect of fish oil supplements is especially important, since TNF α and IL-1 β up-regulated release of collagenase, stromelysin and other enzymes that have been implicated in the irreversible joint damage that is the hallmark of RA.^[5] In contrast, PGE₂ and PGE₃ have similar potency in inducing oedema^[6] and down-regulating TNF α and IL-1 β synthesis by monocytes,^[7] but little, if any, PGE₃ is formed.^[8,9]

Further studies are required to further understanding of the ways in which n-3 LC PUFA alter intracellular signalling and mediator release in monocytes and other cells resident within or infiltrating synovium and other sites of inflammation. Recent studies showing the production of novel anti-inflammatory lipids from EPA via COX in the presence of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)^[10] and from DHA in the presence of aspirin^[11] provide additional candidate mechanisms for the beneficial effects of fish oil in the management of anti-inflammatory diseases, such as RA.

2. Clinical Studies of Fish Oil in Rheumatoid Arthritis (RA)

To date, there have been at least 13 randomised controlled trials of fish oil in RA (table I).^[12-24] All have been undertaken in patients with late disease with mean disease duration of more than 10 years. The most consistent benefits have been reduced morning stiffness and decreased tender joint count. In each of three studies, in which NSAIDs have been given on an as required basis, use of these agents was spared by fish oil (reviewed in James and Cle-

land^[25]). The benefits of fish oil in RA have been endorsed by meta-analysis and mega-analysis.^[26] Importantly, the effects are generally delayed from 2–3 months,^[25,26] as is the case with the disease modifying anti-inflammatory drugs (DMARDs) and in contrast to the immediacy of the analgesic action of NSAIDs. Anti-inflammatory effects have been shown with doses between 2.6 g/day and 7.1 g/day,^[25] but were not seen with a dose of 1.0 g/day.^[23] Kremer and co-workers showed that dose of 90 mg/kg/day EPA/DHA (3 : 2 ratio) was associated with a shorter period to response than 45 mg/kg/day with little additional benefit otherwise.^[14] Thus, higher doses might be considered for loading, with the lesser doses within the anti-inflammatory range for maintenance.

3. Strategies for Implementation in the Clinic

One barrier to the broader use of fish oil in RA is the cost of anti-inflammatory doses when purchased at typical prices for a standard gelatin encapsulated preparation. Pricing for both pharmaceutical and healthcare products appears generally to be pitched toward market tolerance for usual doses. In the case of fish oil supplements, one to two 1g capsules daily is the usual dose for self-medication. As the most commonly used preparations contain 300mg n-3 LC PUFA per gram, this dose falls well short of the doses of more than 2.5g n-3 LC PUFA that have been used in RA studies, which require more than eight capsules daily. For higher doses of n-3 LC PUFA, the cost of fish oil treatment can exceed substantially that of many other medications, and in some jurisdictions may experience a further disadvantage through subsidies for drugs that do not include fish oil.

This extra cost can be largely avoided by using unencapsulated fish oil taken on juice using the 'two glass' technique. This involves floating 10–15mL fish oil on about 30mL of fruit or vegetable juice in a small (e.g. sherry or liqueur) glass. This is placed in the mouth to allow the contents to be swallowed without contacting the lips, thereby avoiding the fish oil taste. Immediately after swallowing, a further

40mL or so of juice is taken from a separate glass to rinse the mouth. If taken before a solid meal without additional fluid, a repeating taste can also be avoided. Lying on the left side for 10 minutes immediately after ingestion in order to drain the stomach

contents into the duodenum is another strategy for avoiding 'repeating' fish oil taste.

However, there is a need to bring more fish body oils to market in unencapsulated liquid form, since cod liver oils, which traditionally have been taken

Table 1. Randomised, controlled trials of fish oil in patients with rheumatoid arthritis

Study	n	Treatment periods (wks)	Medication	Omega-3 fat supplement (g/day)	Outcome measures which improved significantly in the fish oil group
Kremer et al. ^[12]	38	12	Continued	1.8g EPA, 1.2g DHA	No. of tender joints, duration of morning stiffness
Kremer et al. ^[13]	33	14	Continued	2.7g EPA, 1.8g DHA	ARA class, physician's global assessment, no. of tender joints, no. of swollen joints, time to fatigue
Cleland et al. ^[16]	46	12	Continued	3.2g EPA, 2.0g DHA	No. of tender joints, grip strength
Kremer et al. ^[14]	49	24	Continued (change was a withdrawal criterion)	Low dose: 1.7g EPA, 1.2g DHA or high dose: 3.5g EPA, 2.4g DHA ^a	No. of swollen joints, no. of tender joints, grip strength, physician's global assessment, duration of morning stiffness (high dose only)
Tulleken et al. ^[17]	27	12	Continued	2.0g EPA, 1.3g DHA	No. of swollen joints, joint pain index
van der Tempel et al. ^[18]	14	12	Continued	2.0g EPA, 1.3g DHA	No. of swollen joints, duration of morning stiffness
Skoldstam et al. ^[19]	43	24	Continued SAARD. Free to change NSAID	1.8g EPA, 1.2g DHA	Physician global assessment, no. and severity of tender joints (Ritchie Index), decreased NSAID use
Kjeldsen-Kragh et al. ^[20]	67	16	Continued SAARD. NSAID continued in group A and stopped at 10 wks in group B (both groups received n-3 PUFA)	3.8g EPA, 2.0g DHA	No. and severity of tender joints (Ritchie Index), duration of morning stiffness in both groups
Nielsen et al. ^[21]	51	12	Continued (change was a withdrawal criterion)	2.0g EPA, 1.2g DHA	Duration of morning stiffness, no. of tender joints, C-reactive protein levels
Lau et al. ^[22]	64 at entry ^b	52	None on SAARD. Change in NSAIDs was the end-point	1.7g EPA, 1.1g DHA	Reduced NSAID use
Geusens et al. ^[23]	60	52	Varied as required during study	Low dose: 0.86g EPA, 0.18g DHA or high dose: 1.7g EPA, 0.36g DHA	Physician pain assessment, patient global assessment, and decreased NSAID and /or SAARD use (high dose only)
Kremer et al. ^[15]	49	26 or 30	Continued SAARD & NSAID, but NSAID was stopped at 18 or 22 wks	4.6g EPA, 2.5g DHA ^a	No. of tender joints, duration of morning stiffness, physician pain assessment, physician and patient global assessment (all at 18 or 22 weeks)
Volker et al. ^[24]	26	15	Continued (change was a withdrawal criterion). Linoleic acid intake was <10 g/day	1.3g EPA, 1.0g DHA ^a	Within group: swollen joint count, morning stiffness, pain score, physician and patient global assessment, HAQ. Between groups: morning stiffness, HAQ

a Based on 65kg individuals.

b Variable; numbers had dropped at each 3-monthly assessment over a 15-month period.

ARA = American Rheumatoid Association; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **HAQ** = health assessment questionnaire; **n** = No. of participants for analysis; **PUFA** = polyunsaturated fatty acids; **SAARD** = slow acting anti-rheumatic drug.

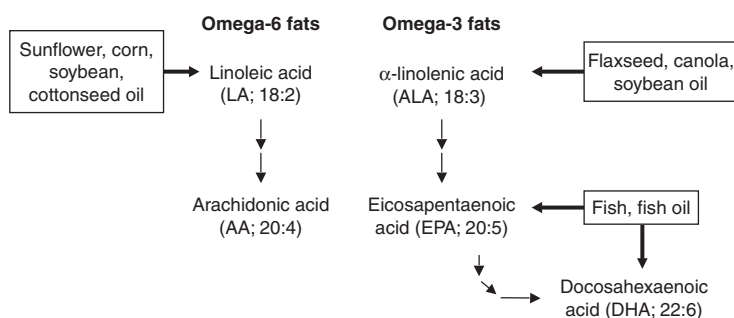


Fig. 3. Metabolism of 18-carbon fatty acids to longer chain fatty acids.

unencapsulated, are often the only fluid preparations available. While fish liver oils are a good source of n-3 LC PUFA (typically 20% w/w), they are also rich in fat-soluble vitamins and some preparations can deliver undesirably high levels of vitamin A at doses that deliver anti-inflammatory quantities of n-3 LC PUFA.

4. Changes in Diet as a Complement to Fish Oil Supplements

While administration of fish oil supplements provides an effective way to increase tissue levels of n-3 LC PUFA, selection of foods rich in n-3 PUFA and avoidance of unnecessary amounts of n-6 PUFA can achieve or facilitate attainment of this end (figure 3).

In the study of Volker et al., patients with RA were selected for an intake of n-6 fats in the background diet of <10 g/day and were given a dose of n-3 LC PUFA of 40 mg/kg/day.^[24] Trials of fish oil in patients with RA have not otherwise addressed the issue of n-6 fat in the background diet. Cleland, James and co-workers in a series of investigations in healthy volunteers, have established that choices of visible fats (spreads, cooking oils, dressing and mayonnaise oils), which are rich in n-3 and monounsaturated fats, with avoidance of products that are rich in n-6 PUFA, can increase tissue EPA levels and/or enhance incorporation of n-3 LC PUFA from fish oil supplements.^[27-29] Use of visible fats rich in n-3 α -linolenic acid (a potential vegetable n-3 precursor of EPA found in flaxseed and some other seed oils) causes a modest increase in EPA relative to that seen with fish oil, but can achieve a measur-

able reduction in the pro-inflammatory cytokines IL-1 and TNF α produced by peripheral blood mononuclear cells *ex vivo*.^[4] Eating fatty fish and manufactured foods, which are enriched in fish oil, also increases tissue n-3 LC PUFA levels and can reduce mononuclear cell IL-1 synthesis.^[28]

Thus, an optimum dietary enrichment strategy will involve the diet *per se*, as well as a fish oil supplement. However, variations in application of this multifactorial dietary approach, coupled with inter-individual putative variability in remodelling dietary C18 n-3 PUFA to n-3 LC PUFA and/or variability in tissue incorporation of dietary n-3 LC PUFA, achieves a range of biochemical outcomes.^[27-29] For this reason, an index of n-3 nutrition is needed for use in the clinic as a guide to the effectiveness and adherence to advice to increase dietary n-3 PUFA intake.

5. Plasma Phospholipid EPA as an Index of Omega-3 Nutrition

With this discussion in section 4 in mind, we have examined plasma phospholipid EPA as a potential index of n-3 nutrition. Our choice of this marker was influenced by our observations that plasma phospholipid EPA level has a very close linear relationship with peripheral blood mononuclear cell (PBMC) phospholipid EPA ($r = 0.97$)^[30] and is easier to measure. PBMC EPA has a significant inverse curvilinear relationship with TNF α and IL-1 β production by these cells.^[4] As discussed in section 1, these cytokines have been implicated as up-regulators of the enzymatic and free-radical mediated destructive events that lead to irreversible

tissue damage in RA and other inflammatory disorders.^[5] We observed that, at PBMC EPA levels of 1.5% total fatty acids or greater, production of these inflammatory cytokines is largely suppressed.^[4] This equates to a plasma phospholipid EPA level of 3.2%, which we have therefore chosen as a notional indicator of effective dietary n-3 PUFA fortification.

We have applied this index in our Early Arthritis Clinic, which has been established to enable early diagnosis and treatment of RA with combination therapy. The treatment regimen involves a combination of drugs (methotrexate, sulfasalazine and hydroxychloroquine in the first instance) coupled with advice to increase n-3 and reduce n-6 PUFA in the diet and to take a fish oil supplement. At first assessment few, if any, patients have plasma phospholipid EPA levels above the target. At 6 and 12 months approximately 60% (n = 24) had levels above target. Some patients had substantially higher levels with a third overall exceeding 5% EPA as a proportion of total plasma phospholipid fatty acids. At 12 months, biochemically validated continuation rate for dietary n-3 PUFA enrichment was similar to admitted continuation rates for sulfasalazine and somewhat less than that for hydroxychloroquine (80%) and methotrexate (96%). Observations have been taken over a period of up to 3 years and raised plasma phospholipid EPA levels have been observed consistently throughout this period in some patients.^[30] Correlations between levels achieved and long-term outcomes in terms of need for escalation of chemotherapy and bone and joint structure and function are the subject of ongoing investigation.

6. Fish Oil Supplements and Cardiovascular Risk in RA

There is now substantial evidence for protective effects of n-3 LC PUFA on the cardiovascular system, with the strongest case being for protection against sudden cardiac death after myocardial infarction^[31] or as a primary event.^[32] This effect is attributable to a membrane stabilising action of n-3 LC PUFA on cardiac myocytes that has been shown in isolated cardiomyocytes and corroborated in

animal studies (see Kang and Leaf^[33] for review) and in preliminary human cardiac electrophysiological studies.^[34] Other observed cardiovascular benefits include reduction of raised plasma triglycerides, a modest reduction in blood pressure, and an amelioration of the effects of atherogenic diets in experimental animals (see O'Keefe and Harris^[35] for review). These considerations are especially pertinent in RA, in which the incidence of cardiovascular events is increased to an extent that reducing cardiovascular events should be seen as component of the management of RA.^[36]

7. Fish Oil and Diet Drug Interactions

There are a number of potentially favourable interactions between fish oil treatment and chemotherapy in RA. These include reduced NSAID use (discussed in section 2), and amelioration of the dose limiting nephrotoxic and hypertensive effects of cyclosporin A.^[37] There are several anti-rheumatic agents with the potential to increase cardiovascular risk. These include the highly selective COX-2 inhibitors, which can dysregulate TXA₂/PGI₂ balance in favour of prothrombotic TXA₂,^[38] an effect likely to be reduced by dietary fortification with n-3 LC PUFA. The combination of methotrexate and sulfasalazine elevates plasma homocysteine levels,^[39] a risk factor for cardiovascular disease. Corticosteroids increase vascular risk and reduce bone density.^[40] Preliminary data suggest dietary n-3 LC PUFA may have a favourable effect on bone density.^[41] Finally, supplementation with dietary n-3 LC PUFA, by virtue of its ability to inhibit TNF α and IL-1 β synthesis, is a logical, inexpensive companion intervention for highly expensive biological agent therapies that have been designed to block these cytokines.

8. Recent Onset RA

Studies of fish oil in RA to date have dealt principally with late disease. The use of fish oil remains to be evaluated within the context of best practice combination treatment of recent onset RA.^[42] Ideally treatment should be introduced within 3–4 months of onset. The complexity of early

management of RA and assessment of long-term outcomes gives impetus to implementation within the trial setting of an index of n-3 nutrition as discussed in section 5. End points for correlative analyses should include the need for escalation of treatment according to predetermined criteria, unwanted events, peri-articular bony erosions and peri-articular and more remote bone density, functional outcomes, including activities of daily living and participation in paid employment. These studies will need to be well designed and multicentred. Studies that evaluate rules for applying combinations of agents of known efficacy in series or in parallel are difficult intrinsically, but are crucial to the definition of orderly treatment that achieves best outcomes. In the case of dietary n-3 fats, biochemical effects are likely to be more readily established than correlations with clinical effects, although logically one would expect these to follow.

9. Other Applications

9.1 Inflammatory Diseases

Lessons learned in the practice of introducing fish oil in RA should be extended to management and trials of other inflammatory diseases. The reported favourable influence of fish oil on relapse rates in Crohn's disease^[43] and progression rates in IgA nephropathy^[44] warrants further attention. The known cardiovascular benefits of n-3 LC PUFA and beneficial effects of fish oil diets on disease manifestations and survival in lupus mice^[45] suggest studies into the influence of fish oil supplements on long-term renal outcomes and cardiovascular events in systemic lupus could be rewarding. The positive results of infusions with n-3 LC PUFA in patients with psoriasis^[46] suggest a novel approach to treating psoriatic arthritis, which can be resistant to usual anti-rheumatic treatments.

9.2 Osteoarthritis

The possible influence of dietary n-3 LC PUFA on the occurrence and progression of osteoarthritis (OA) is an obvious and neglected question. The inhibitory effects of n-3 LC PUFA on release by

chondrocytes of enzymes implicated in the pathogenesis of OA^[47] provides ample rationale for a trial. To date, there are no *in vivo* data from animal or human studies that address this question. Considering the emerging basis for broad recommendations to increase dietary n-3 PUFA intakes for cardiovascular benefit, the possible positive or negative effects of fish oil/n-3 LC PUFA on OA need to be defined. However, the nature of these assessments is such that studies need to be designed carefully and prospectively. The prevalence of OA is sufficient to make an analysis of effects on OA potentially feasible within the context of a large long-term intervention study into the effects of fish oil on cardiovascular outcomes (e.g. primary sudden cardiac death) in elderly individuals.

10. Barriers to Implementation

In seeking to promote the use fish oil supplements in the clinical situation where benefit has been shown, one needs to consider a number of barriers to implementation. Not least is the pervasive influence that drug company marketing has on the continuing education of physicians. Messages about the health benefits of n-3 LC PUFA must compete at a disadvantage with the sophisticated and lavishly resourced promotions for patented prescription medications. A related problem is the lack of instructional skills among physicians with regard to the theoretical and practical aspects of dietary n-3 PUFA enrichment. There is also the issue of the opportunity costs for doctors who commit to detailed explanations about diet. Patients can be daunted by substantial procurement costs for fish oil capsules, which may not be covered by pharmaceutical subsidy arrangements. Suitable unencapsulated fish body oil preparations and broader education in the 'two glass' technique would help resolve this problem. Finally, there is the lack of short-term therapeutic targets for a treatment with delayed effects. It is in relation to the latter that the proposed index of n-3 nutrition may be especially useful. If validated, a target EPA level, or a related index, could prove as useful as other indices used to reduce long-term risks for unwanted events associated with

chronic disordered homeostasis. In this regard there are parallels with now standard medical measures such as blood pressure, blood lipids (cholesterol and triglycerides) and glycosylated haemoglobin.

11. Conclusion

There exist high level standards of evidence for clinically beneficial effects of dietary fish oil in inflammatory disease, particularly RA. The barriers to uptake of this approach in the standard treatment of RA are not difficult to discern and they involve a mix of issues ranging from a marketing vacuum due to a lack of patentability of fish oil (and fish) to physical and financial barriers in ingesting daily anti-inflammatory doses of fish oil. However, use of bulk fish oils can overcome the latter two issues. In addition, use of an index of n-3 nutrition can provide helpful feedback to both patients and clinicians on the success of the intervention in attaining target levels.

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