

Fish Oil and Osteoarthritis: Current Evidence

Chelsea Boe, MD, and C. Thomas Vangsness, MD

Abstract

According to the 2005 US census, osteoarthritis (OA) was the leading cause of disability in the United States, affecting more than 50 million people. Current treatments are targeted at reducing symptoms of the inflammatory reaction that occurs after destruction of essential joint cartilage. However, these treatments do not prevent significant pain and activity restriction.

We reviewed the literature to address claims that fish oil supplementation can prevent or decrease severity of OA. Our extensive search of databases covered all relevant terms related to omega-3-containing supplements and their effects on OA. We hypothesized there would be insufficient clinical

studies to justify recommending supplementation to patients.

Laboratory studies have shown that eicosapentaenoic acid and docosahexaenoic acid reduce proinflammatory mediators and increase joint lubrication in vitro. In addition, canine trials have shown clinically significant reductions in various symptom parameters. Results of human clinical trials have not been consistently significant.

Well-designed clinical trials are needed to substantiate or refute the potential benefit of fish oils in OA treatment. Long-term studies are needed to assess the possibility of prevention. In addition, standardization of the fish oil industry is needed for consistency of therapy.

First-line treatments for osteoarthritis (OA) are targeted at the inflammatory reaction that occurs after breakdown of articular cartilage through regular use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, or surgical intervention. Associated activity restrictions and chronic pain have spurred a search for alternative treatments, commonly daily supplements such as glucosamine, chondroitin, and fish oil, to name a select few of the innumerable products reported to benefit patients with OA.

Background

Fish oil is 1 of the 2 most popular supplements among patients with OA. However, its effectiveness and precise benefit are still debated,^{1,2} and there is confusion about the definition of the product, the nature of investigations into its effectiveness, and the standardization of research unique to OA. Most fish oil research relates to patients with rheumatoid arthritis (RA). The anti-inflammatory benefits seen in patients with RA are generally applied to characterize fish oils as anti-inflammatory agents with a logical benefit in reducing OA symptoms. However, there is a dearth of independent and focused clinical results justifying that assumption. Further, lack of federal regulation of the supplement industry hinders conducting generalizable studies regarding medical benefit in a regulated and verified dose and form.³

The benefits of fish oil in RA treatment are well supported

and accepted. In patients with RA, daily fish oil supplementation has been shown to reduce use of other medications and improve pain scores reported by both physicians and patients.⁴⁻¹⁰ The clinical efficacy of fish oil use in RA has been determined to be “reasonably strong,” with multiple studies confirming suppression of inflammatory cytokines in vitro and in vivo.^{11,12} The mechanism by which the inflammatory processes are augmented by fish oil supplementation suggests potential benefit to patients with OA, though review articles as recent as 2011 have concluded that research in that capacity is not sufficient to warrant recommendation.^{13,14}

Most studies of OA-specific use of fish oils have been conducted in in vitro models. Treatment of bovine chondrocytes with omega-3 fatty acids causes reductions in inflammatory markers induced by interleukin 1, one of several proinflammatory cytokines that induce inflammation in OA at the gene and plasma levels, and these reductions have been reproduced.¹⁵⁻¹⁷ Although a preventive benefit was found in a study of pig medial collateral ligament fibroblasts, findings of later studies have been inconsistent.¹⁸ It also appears that fish oils may alter lipid composition in membranes, favoring incorporation of anti-inflammatory precursor n-3 fatty acids over proinflammatory precursor n-6 fatty acids in these model systems.^{19,20}

Animal in vivo models have also been used to describe the effects of fish oil supplementation on OA. Assessment of dogs

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with OA before and after supplementation with the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) revealed improvement in clinical signs observed by owners, improvement in weight-bearing measured by veterinary clinicians, and decreased use of NSAIDs.²¹⁻²⁴

Fish oil studies using osteoarthritic cartilage samples harvested during surgical procedures have demonstrated results consistent with other model systems described thus far. They have demonstrated a dose-dependent decrease in induced inflammatory destruction of tissue associated with fish oil supplementation. In addition, finding a lack of cellular toxicity, they have validated the safety of supplements.^{25,26} Proposed but unproven mechanisms for the anti-inflammatory actions of EPA and DHA include competition with n-6 fatty acids; presence of resolvins (anti-inflammatory molecules derived from EPA and DHA); presence of n-3 products that compete with proinflammatory molecules for receptors; reduction in gene expression of cytokines, cyclooxygenase 2, and degrading proteinases; interference in the signaling pathways of inflammation; and reduction in lymphocyte proliferation.^{26,27}

Reduction in the n-6/n-3 ratio has been correlated with reduced inflammatory conditions such as OA, stemming from the epidemiologic evidence that higher n-3 intake in Eastern diets and lower intake of n-6 result in a lower incidence of these diseases.^{18,28,29} Studies have found sufficient evidence to suggest that this ratio has a role in OA, though not sufficient to recommend supplement use over diet modification.¹⁹ One study demonstrated an ability to favorably alter bone marrow lipid composition with n-3 fatty acid supplementation.¹⁰

The evidence leads to a conclusion of anti-inflammatory benefits from fish oils in these abstracted models. The multitude of basic science studies conducted on the anti-inflammatory properties of omega-3 fatty acids, only briefly reviewed here, supports the potential benefits colloquially ascribed to fish oil in the treatment of OA yet also implies the need for human clinical trials to address these properties clinically.

We reviewed the literature to address claims that fish oil supplementation can prevent or decrease severity of OA. We hypothesized there would be insufficient clinical studies to justify recommending supplementation to patients. Of note, the degree of heterogeneity in the evidence precluded performing a meta-analysis with any statistical validity.

Literature Review

In the PubMed database, we targeted the subject of fish oils and OA by using search terms that included omega-3, DHA, EPA, and alpha-linolenic acid. The MedLine and Google Scholar databases were searched as well. Results were limited to those reported in English and involving human subjects and clinical trials; results were excluded if they primarily involved patients with RA. Studies cited or mentioned in articles found through the PubMed search were evaluated according to the criteria mentioned, such that all relevant articles available at time of search are thought to be included, and these articles represent a reasonable presentation of the available evidence.

Findings

Our search revealed 6 clinical trials in which omega-3-containing supplements were used in the treatment of human OA with differing endpoints. We reviewed these trials in detail. One study, which used alteration of bone marrow lipids as an endpoint, was included for completeness of the evaluation of the relevant evidence.²⁰ In addition, the study by Wang and colleagues,³⁰ who assessed patients without clinical evidence of OA for development of bone marrow lesions, was reviewed. This study was deemed relevant to examine the process by which n-3 fatty acids alter knee structure, as subsequent risk of OA has not been elucidated, and effects on bone marrow lesions may indeed have a direct impact on the OA process. Results of the trials that were identified were varied between no significant difference in OA symptoms between treatment and control groups, implied benefits, and substantial benefits.

The first clinical study of omega-3 supplementation in OA treatment was conducted in 1992.³¹ The study compared 10 g of cod liver oil (containing 786 mg of EPA) with 10 g of olive oil, both taken daily over 24 weeks by 86 patients with OA. Effects were assessed by NSAID use (recorded in patient diary) and pain score (evaluated by clinician) every 4 weeks. The trial found no significant difference in effects between the oils.

Wang and colleagues³⁰ used a food questionnaire to measure the n-3 intake of 293 healthy adults and quantified their bone marrow lesions after 10 years in an effort to describe how n-3 intake correlates with development of OA or pre-OA lesions. Higher intake of n-6 fatty acids was positively associated with presence of bone marrow lesions; n-3 intake had no association.

In a study of 84 patients who had joint replacement, Pritchett²⁰ evaluated lipid alterations resulting from a regimen of 3 g of fish oil containing 11% DHA daily for a 6-month trial period, measuring lipids before and after the trial period. Pritchett²⁰ found a 20% increase in long-chain fatty acids and a corresponding decrease in saturated fatty acids, as measured in bone marrow.

The supplement Phytalgic (Phythea Laboratories), which is advertised for OA, includes n-3 fatty acids, n-6 fatty acids, extract from *Urtica dioica* (the common nettle), zinc, and vitamin E. In a study by Jacquet and colleagues,³² this supplement was given 3 times daily over 3 separate 4-week periods to 81 patients with knee or hip OA. Measuring NSAID use with patient diaries and assessing pain with the WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index every 4 weeks for 12 weeks, the authors found a significant decrease in NSAID use and, according to WOMAC results, a more than 50% reduction in pain and stiffness, and improved function.

One study compared the effects of glucosamine with and without omega-3 fatty acids in 182 patients with knee or hip OA.³³ Each day, patients took 500 mg of glucosamine plus 3 capsules each containing either 444 mg of omega-3 fatty acids or 444 mg of an oil mixture. Pain was assessed with visual analog scale and the WOMAC scale 3 times over the 26-week

study. More than 90% reductions in morning stiffness and pain were found for the combination of fish oil and glucosamine.

The Multicenter Osteoarthritis Study (MOST), published in February 2012, demonstrated that plasma levels of n-3 and n-6 polyunsaturated fatty acids (PUFAs) may be related to knee structural findings.³⁴ This study confirmed that dietary modification of n-3 and n-6 PUFAs altered plasma concentration predictably. Higher DHA intake was associated with less evidence of OA on patellofemoral cartilage, though no association was found on tibiofemoral cartilage.³⁴

Discussion

The lack of human clinical trials detailing the effects of fish oil supplementation in patients with OA is arguably the most significant hindrance to fish oil being routinely recommended. Since 1992, only 6 studies have addressed this topic, and their endpoints and results were inconsistent. These interventional trials had their limitations, including short duration, insufficient dosage, inappropriate n-3 choice, dietary interactions, genotype, and medication interactions.¹⁸ The present review is limited as well, by the quantity of evidence on the topic and by the focus (of the majority of the studies) on short-term alterations in pain and mobility instead of on disease-modifying potential. Short-term evaluation is unlikely to capture such an effect, which may require long-term supplementation to become evident.

The results of the study by Stammers and colleagues³¹ must be examined critically, as the likelihood of detection bias is high. Highly subjective assessments of effect, lack of standardized NSAID treatments, and limitations in patient numbers and disease severity raise concerns about validity. In addition, confounding variables (eg, medication interactions, alternative treatments, olive oil use) undermine the design. It is therefore difficult to interpret the results of this trial.

The study by Wang and colleagues³⁰ did not involve supplementation, and intake was assessed only with food frequency questionnaires. It is therefore difficult to apply their results or findings to this review. In addition, the authors did not obtain baseline magnetic resonance imaging for comparison with that obtained at study completion—that is, they did not address any subclinical disease before dietary recording.

Pritchett²⁰ acknowledged study limitations of small sample size and use of 1 subject as both patient and control. Although the study seemed to demonstrate that omega-3 supplementation augmented the lipid profile of joints, it did not directly demonstrate improvement in or prevention of OA. Identification of bone marrow lesions is not definitive proof of OA but an alteration that may correlate with development. The logical supposition is that altering the local environment may alter development of disease within that environment, though this is not proven.

An article reviewing the Phytalgic study highlighted the suspect nature of its results—claims that the supplement is 76% more effective than gold-standard corticosteroid injection.³⁵ Also highlighted were lack of confirmed mechanism, questionable control, detection bias caused by aftertaste, and the high attrition rate in the placebo group. It is difficult to

apply these results to fish oil supplementation, as Phytalgic contains other potentially confounding substances.

Of note, the findings of MOST were observational; n-3 and n-6 levels were not altered or supplemented. Altered disease process was demonstrated in patellofemoral cartilage but not in tibiofemoral cartilage in the same patient. The inconsistencies may be explained by the observational nature of the study and the lack of supplementation that would have produced a more significant increase in n-3 PUFA levels and thus more uniform conclusions, if in fact n-3 PUFAs were the significant factor in the altered cartilage structure. Although supportive of a preventive or disease-altering benefit, the results do not speak to supplementation.

Perhaps the most convincing evidence supporting fish oil for OA comes from a 2009 study by Gruenwald and colleagues.³³ However, this 2-supplement study addressing synergy was financed by Seven Seas, a company with industry ties. The study was not placebo-controlled and was registered only after completion. The authors omitted baseline values, apparently did not correct for baseline in the statistical analysis, and did not report the distribution of results. The implication is that the results were overstated, or that, at minimum, the supporting data were not reported. Nevertheless, this study demonstrated benefits consistent with the animal and human laboratory studies. However, research is needed to repeat and validate these results, elucidate the mechanism of action, and quantify the benefit unique to fish oil.

Conclusion

Despite the overwhelming popularity of fish oil supplements and the assumption of benefit for patients with arthritis, there appears to be insufficient clinical evidence to justify use of fish oils in the treatment or prevention of OA. Possible efficacy in laboratory and animal studies has yet to be sufficiently observed and verified in clinical trials. Although it is impossible to refute the promise of these agents as beneficial adjuncts to anti-inflammatory regimens, there remains a need for significant, well-designed clinical trials to evaluate the efficacy, safety, and clinical parameters of omega-3 fatty acids in a standardized form before they can in good faith be recommended to patients with OA.

Dr. Boe is Resident Physician, Department of Orthopaedic Surgery, Mayo School of Graduate Medical Education, Rochester, Minnesota. Dr. Vangsness is Professor of Orthopaedic Surgery and Chief of Sports Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.

Address correspondence to: Chelsea Boe, MD, Mayo School of Graduate Medical Education, Gonda 14, 200 First St SW, Rochester, MN 55905 (tel, 507-284-1208; email, boe.chelsea@mayo.edu).

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References

- Jordan KM, Sawyer S, Coakley HE, Smith HE, Cooper C, Arden NK. The use of conventional and complementary treatments for knee osteoarthritis in the community. *Rheumatology.* 2003;43(3):381-384.
- Vista ES, Lau CS. What about supplements for osteoarthritis? A critical and

- evidenced-based review. *Int J Rheum Dis*. 2011;14(2):152-158.
3. European Food Safety Authority Panel on Biological Hazards (BIOHAZ). Scientific opinion on fish oil for human consumption. Food hygiene, including rancidity. *EFSA J*. 2010;8(10):1874.
 4. Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. *Nutrition*. 2005;21(2):131-136.
 5. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006;83(6 suppl):1505S-1519S.
 6. Calder PC, Zurier RB. Polyunsaturated fatty acids and rheumatoid arthritis. *Curr Opin Clin Nutr Metab Care*. 2001;4(2):115-121.
 7. Kremer JM. Effects of modulation of inflammatory and immune parameters in patients with rheumatic and inflammatory disease receiving dietary supplementation of n-3 and n-6 fatty acids. *Lipids*. 1996;31(suppl):S243-S247.
 8. Kremer JM, Jubiz W, Michalek A, et al. Fish oil fatty acid supplementation in active rheumatoid arthritis. A double-blinded, controlled, crossover study. *Ann Intern Med*. 1987;106(4):497-503.
 9. Kremer JM, Lawrence DA, Jubiz W, et al. Dietary fish oil supplementation in patients with rheumatoid arthritis. Clinical and immunologic effects. *Arthritis Rheum*. 1990;33(6):810-820.
 10. Nielsen GL, Faarvang KL, Thomsen BS, et al. The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. *Eur J Clin Invest*. 1992;22(10):687-691.
 11. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain*. 2007;129(1-2):210-223.
 12. van der Tempel H, Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. Effects of fish oil supplementation in rheumatoid arthritis. *Ann Rheum Dis*. 1990;49(2):76-80.
 13. Rosenbaum CC, O'Mathúna DP, Chavez M, Shields K. Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis. *Altern Ther Health Med*. 2010;16(2):32-40.
 14. Sanghi D, Avasthi S, Srivastava RN, Singh A. Nutritional factors and osteoarthritis: a review article. *Internet J Med Update*. 2009;4(1).
 15. Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J Biol Chem*. 2000;275(2):721-724.
 16. Curtis CL, Rees SG, Cramp J, et al. Effects of fatty acids on cartilage metabolism. *Proc Nutr Soc*. 2002;61(3):381-389.
 17. Zainal Z, Longman AJ, Hurst S, et al. Relative efficacies of omega-3 polyunsaturated fatty acids in reducing expression of key proteins in a model system for studying osteoarthritis. *Osteoarthritis Cartilage*. 2009;17(7):896-905.
 18. Hankenson KD, Watkins BA, Schoenlein IA, Allen KG, Turek JJ. Omega-3 fatty acids enhance ligament fibroblast collagen formation in association with changes in interleukin-6 production. *Proc Soc Exp Biol Med*. 2000;223(1):88-95.
 19. Melanson KJ. Diet, nutrition and osteoarthritis. *Am J Lifestyle Med*. 2007;1(4):260-263.
 20. Pritchett JW. Statins and dietary fish oils improve lipid composition in bone marrow and joints. *Clin Orthop Relat Res*. 2007;(456):233-237.
 21. Roush JK, Cross AR, Renberg WC, et al. Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. *J Am Vet Med Assoc*. 2010;236(1):67-73.
 22. Roush JK, Dodd CE, Fritsch DA, et al. Multicenter veterinary practice assessment of the effects of omega-3 fatty acids on osteoarthritis in dogs. *J Am Vet Med Assoc*. 2010;236(1):59-66.
 23. Fritsch DA, Allen TA, Dodd CE, et al. A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis. *J Am Vet Med Assoc*. 2010;236(5):535-539.
 24. Fritsch DA, Allen TA, Dodd CE, et al. Dose-titration effects of fish oil in osteoarthritic dogs. *J Vet Intern Med*. 2010;24(5):1020-1026.
 25. Curtis CL, Rees SG, Little CB, et al. Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis Rheum*. 2002;46(6):1544-1553.
 26. Shen CL, Dunn DM, Henry JH, Li Y, Watkins BA. Decreased production of inflammatory mediators in human osteoarthritic chondrocytes by conjugated linoleic acids. *Lipids*. 2004;39(2):161-166.
 27. Hurst S, Zainal Z, Caterson B, Hughes CE, Harwood JL. Dietary fatty acids and arthritis. *Prostaglandins Leukot Essent Fatty Acids*. 2010;82(4-6):315-318.
 28. Cleland LG, Hill CL, James MJ. Diet and arthritis. *Baillieres Clin Rheumatol*. 1995;9(4):771-785.
 29. Maresz K, Meus K, Porwolik B. Krill oil: background and benefits. *Int Sci Health Found*. 2010;1-11.
 30. Wang Y, Wluka AE, Hodge AM, et al. Effect of fatty acids on bone marrow lesions and knee cartilage in healthy, middle-aged subjects without clinical knee osteoarthritis. *Osteoarthritis Cartilage*. 2008;16(5):579-583.
 31. Stammers T, Sibbald B, Freeling P. Efficacy of cod liver oil as an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. *Ann Rheum Dis*. 1992;51(1):128-129.
 32. Jacquet A, Girodet PO, Pariente A, Forest K, Mallet L, Moore N. Phytalgic, a food supplement, vs placebo in patients with osteoarthritis of the knee or hip: a randomised double-blind placebo-controlled clinical trial. *Arthritis Res Ther*. 2009;11(6):R192.
 33. Gruenewald J, Petzold E, Busch R, Petzold HP, Graubaus HJ. Effect of glucosamine sulfate with or without omega-3 fatty acids in patients with osteoarthritis. *Adv Ther*. 2009;26(9):858-871.
 34. Baker KR, Matthan NR, Lichtenstein AH, et al. Association of plasma n-6 and n-3 polyunsaturated fatty acids with synovitis in the knee: the MOST study. *Osteoarthritis Cartilage*. 2012;20(5):382-387.
 35. Christensen R, Bliddal H. Is Phytalgic® a goldmine for osteoarthritis patients or is there something fishy about this nutraceutical? A summary of findings and risk-of-bias assessment. *Arthritis Res Ther*. 2010;12(1):105.

This paper will be judged for the Resident Writer's Award.
