

Review Article

The impact of fish oil supplementation in patients with rheumatoid arthritis

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ABSTRACT

Many clinical trials of omega-3 fatty acids, supplied as fish oil supplements, have been carried out in rheumatoid arthritis (RA) over the past 3 decades. The current analysis evaluates the influence of omega-3 polyunsaturated fatty acids on clinical results in patients with rheumatoid arthritis. We conducted the current meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 31 January 2018 for randomized controlled trials that examined the influence of omega-3 PUFAs on clinical results in patients with rheumatoid arthritis. We identified 8 prospective studies that could be included in the meta-analysis. They showed that omega-3 PUFAs had a clear influence on NSAID consumption (SMD -0.52, 95% CI -0.92 to -0.12, $p = 0.01$) without between-study heterogeneity ($I^2 = 0\%$) and in pain (SMD -0.55, 95% CI 0.17-0.027, $p = 0.57$). The use of omega-3 PUFAs at dosages of >2.7 g/day for more than three months can be effective at decreasing NSAID use in rheumatoid arthritis patients.

Keywords: Meta-analysis, Omega-3 polyunsaturated fatty acids, Rheumatoid arthritis

INTRODUCTION

Fish oil is rich in omega-3 fatty acids, which are part of a key family of polyunsaturated fatty acids (PUFAs). Both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are important omega-3 fatty acids that are primarily derived from marine-based sources.¹ Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. An external trigger (e.g., cigarette smoking, infection, or trauma) that

triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.²

Fatty acids are categorized into omega-6 or omega-3 polyunsaturated fatty acids (PUFAs) series liable on the situation at which the first double bond from the methyl end happens. The omega-6 series fatty acids include linoleic acid (LA) and arachidonic acid (AA), and the

omega-3 fatty acids include α -linolenic acid (ALA), docosahexaenoic acid, and eicosapentaenoic acid (EPA). As both fatty series are metabolized by mutual enzymes (elongases and desaturases), a competitive interaction occurs amongst the fatty acids: the omega-3 PUFA family suppresses the metabolism of the omega-6 PUFA family, and vice versa, while the suppression in the latter case is to a reduced level.³ Eicosapentaenoic acid and docosahexaenoic acid inhibit activation of the nuclear factor κ B (NF- κ B) and publication of tumor necrosis factor α (TNF- α) and interleukin-1 beta (IL-1 β).^{4,5}

It has been recommended that the symptomatic advantage of a day-to-day omega-3 PUFA consumption of >2.7 g/day can be overdue and take 2–3 months, and a daily omega-3 PUFA consumption is necessary to attain anti-inflammatory effects.⁶ The main benefit of meta-analysis is that it increases sample size, which probably decreases the possibility that random fault will yield false-positive or -negative relations.⁷ Consequently, the purpose of the current meta-analysis was to examine the influence of a day-to-day omega-3 polyunsaturated fatty acids intake for more than three months on clinical results in patients with rheumatoid arthritis.

METHODS

Data sources and searches

We conducted the current meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 31 January 2018 for randomized controlled trials that examined the influence of omega-3 PUFAs on clinical results in patients with rheumatoid arthritis. Both semiparametric and parametric methods were used. No language restrictions were imposed.

Selection criteria

Studies were included in this meta-analysis if they satisfied the following criteria: RCTs which examine the influence of a day-to-day omega-3 polyunsaturated fatty acids intake for more than three months on clinical results in patients with rheumatoid arthritis, all of whom were randomized to receive treatment or placebo. The investigators reported relative risks (RRs) with 95% CI.

Data extraction

The final data were abstracted from each study using standardized form: the first author's name, year of publication, number of patients, age, study location, follow-up duration, NSAID intake, and duration of illness. These factors were chosen because they represent the most important variables for assessing patient risk and treatment of patients. Flow diagram showing the selection criteria of assessed studies.⁸

Statistical analysis

The present meta-analysis utilized Stata version 12.0 software for statistical analysis. Mean difference (MD) were calculated for continuous variables. Pooled odds ratios (OR) were calculated for discrete variables. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test with a significance set at the P-value <0.10 or I^2 score >50%.⁹ DerSimonian-Laird random-effect meta-analysis was adopted when obvious heterogeneity existed.¹⁰

RESULTS

We recognized 245 citations using the search strategy. Of these, we excluded 151 after examining the title and abstract including removal of duplicates. We retrieved and evaluated 15 articles in more detail, of which 7 articles were excluded, leaving 8 studies that were eligible for inclusion (Figure 1). Main characteristics of included studies have been summarized in Table 1.

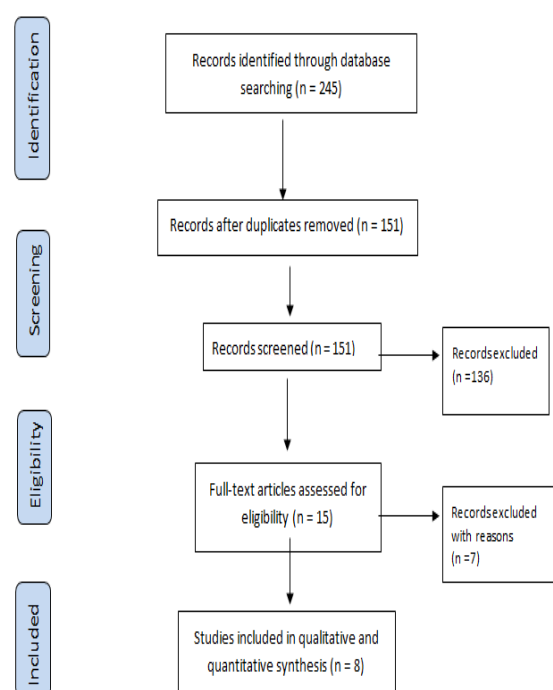


Figure 1: Flow diagram showing the selection criteria of assessed studies.

Two of the eight studies comprised examined NSAID consumption. No significant development was perceived in the omega-3 PUFA group as compared with controls for any clinical results excluding decreased NSAID consumption. Pain (SMD−0.55, 95% CI 0.17–0.027, $p=0.57$) (Table 2).

Meta-analysis showed that omega-3 PUFAs had a clear influence on NSAID consumption (SMD-0.52, 95% CI

-0.92 to -0.12, $p=0.01$) without between-study heterogeneity ($I^2=0\%$) (Table 3).

Table 1: Main characteristics of included studies.

| Study | Year | Follow-up duration | Disease duration | Omega-3 PUFAs dose (g/day) |
|--------------------------|------|--------------------|------------------|-----------------------------------|
| Nielsen ¹¹ | 1992 | 3 months | 5 (1–41) | 3.2 (2.0 g EPA, 1.2 g DHA) |
| French ¹² | 1988 | 3 months | 8.0 (1–22) | 5.2 (3.2 g EPA, 2.0 g DHA) |
| Morley ¹³ | 1993 | 15 months | 4.7 (1–18) | 2.9 (1.71 g EPA, 1.14 g DHA) |
| Skoldstam ¹⁴ | 1992 | 6 months | 18 (4–41) | 3.0 (1.8 g EPA, 1.2 g DHA) |
| Berbert ¹⁵ | 2005 | 6 months | 15±12 | 3.0 (1.8 g EPA, 1.2 g DHA) |
| Limburg ¹⁶ | 1990 | 3 months | 18 (6–30) | 3.4 (2.04 g EPA, 1.32 g DHA) |
| Sundrarjun ¹⁷ | 2004 | 6 months | 4.4±1.9 | 3.4 (1.88 g EPA, 1.48 g DHA) |
| Kremer ¹⁸ | 1990 | 6 months | 12.8 (1–30) | >2.7 (54 mg/kg EPA, 36 mg/kg DHA) |

Table 2: The effect of omega-3 polyunsaturated fatty acids on pain.

| Study | SMD | 95% CI |
|--------------------------|-------|-------------|
| Nielsen ¹¹ | -0.30 | (0.22–0.82) |
| French ¹² | -0.02 | (0.56–0.61) |
| Skoldstam ¹⁴ | 0.03 | (0.63–0.57) |
| Berbert ¹⁵ | -0.61 | (0.19–1.39) |
| Limburg ¹⁶ | -0.26 | (0.50–1.02) |
| Sundrarjun ¹⁷ | 0.66 | (1.25–0.07) |
| Kremer ¹⁸ | 0.27 | (1.25–0.48) |
| Total | -0.55 | (0.17–0.27) |

Table 3: The effect of omega-3 polyunsaturated fatty acids on NSAID consumption.

| Study | SMD | 95% CI |
|-------------------------|-------|--------------|
| Skoldstam ¹⁴ | 0.63 | (-0.02–1.25) |
| Morley ¹³ | -0.44 | (0.09–0.96) |
| Total | -0.52 | (-0.12–0.92) |

DISCUSSION

Omega-3 PUFAs were not found to improve clinical outcome measures except for NSAID consumption. NSAID requirements were significantly lesser in the omega-3 PUFAs group than in placebo-treated controls; therefore, our results propose that taking omega-3 PUFAs at dosages of >2.7 g/day for more than three months decreased NSAID intake in rheumatoid arthritis patients. Additionally, studies by Galarraaga et al and Adam et al. also showed a reduction in the daily requirement of NSAIDs in rheumatoid arthritis, while the information were not encompassed in the current study as they did not meet inclusion criteria.^{19,20} This result is significant since there are growing worries regarding the contrary influence of NSAIDs, which are the most regularly recommended medication for rheumatoid arthritis patients.

Acute presentations in patients with RA are commonly due to an exacerbation of known disease or manifestations in other organ systems or other disease sequelae. Patients presenting with an initial onset of

previously undiagnosed possible RA require symptomatic treatment with NSAIDs and rapid referral for definitive diagnosis and institution of DMARD therapy. A delay of as little as 2-3 months in initiating joint-sparing therapy results in significant irreversible joint damage measured radiographically at 5 years. In patients with known disease, increased pain, edema, and dysfunction are characteristics of rheumatoid flare (exacerbation). Flares may be local or systemic in nature. Laboratory evaluation may reveal elevation in acute-phase reactants. Treatment consists of rest, NSAIDs, DMARDs, short courses of steroids (2-4 weeks), and, possibly, intra-articular steroid injections. Pain relief is important and may necessitate short-term use of narcotic analgesics.^{21,22} The relation between omega-3 PUFAs and NSAID consumption was based on meta-analysis of only two case-control studies. Use of NSAIDs was reduced, but clinical outcomes were not improved significantly. This appears counter-intuitive as NSAID utilized by patients is to decrease pain. Consequently, further studies are required to answer the question as to whether omega-3 PUFAs reduce NSAID requirements in rheumatoid arthritis patients.

Omega-3 PUFAs might lessen pain and inflammation in RA through the following mechanisms. Omega-3 PUFAs competitively constrain the creations of PGE2 and LTB4, which in turn constrain the triggering of the NF- κ B, and consequently the discharge of the inflammatory cytokines such as IL-1 β and TNF- α . RA is related with a 2-fold increase in cardiovascular mortality. Fish oil has a favorable effect on plasma lipids and reduces blood pressure through vascular PGI2 synthesis. Reduced arterial stiffness and antiarrhythmic effect are other benefits of fish oil. Therefore, fish oil can decrease CV risk in rheumatoid arthritis patients.²³

CONCLUSION

The use of omega-3 PUFAs at dosages of >2.7 g/day for more than three months can be effective at decreasing NSAID use in rheumatoid arthritis patients. Nevertheless, further studies should be made to make a better understanding of the potential biological mechanisms. Large-scale and long-term randomized controlled trials in various populations must be carried out in future studies to deliver more significant evidence.

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Ethical approval: Not required

REFERENCES

- Shahidi F, Miraliakbari H. Omega-3 (n-3) fatty acids in health and disease: part 1—cardiovascular disease and cancer. *J Med Food*. 2004;7:387–401.
- Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569–81.
- Kelley DS. Modulation of human immune and inflammatory responses by dietary fatty acids. *Nutrition*. 2001;17:669–73.
- Calder PC. N-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006;83:1505–19.
- Novak TE, Babcock TA, Jho DH, Helton WS, Espat NJ. NF-kappa B inhibition by omega -3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. *Am J Physiol Lung Cell Mol Physiol*. 2003;284:84–9.
- 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):210–23.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315(7121):1533–7.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2007.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. 2008.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–88.
- Nielsen GL, Faarvang KL, Thomsen BS, Teglbjaerg KL, Jensen LT, Hansen TM, 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):687–91.
- French JK, Cleland LG, Betts WH, Murphy GA, Elliott MJ. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. *J Rheumatol*. 1988;15(10):1471–5.
- Morley KD, Lau CS, Belch JJ. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis—a double-blind placebo controlled study. *Br J Rheumatol*. 1993;32(11):982–9.
- Sködstam L, Börjesson O, Kjällman A, Seiving B, Akesson B. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. *Scand J Rheumatol*. 1992;21(4):178–85.
- 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):131–6.
- Van der Tempel H, Tulleken JE, Limburg PC, Muskiet FAJ, Van Rijswijk MH. Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis Rheum*. 1990;33:1416–9.
- Sundrarjun T, Komindr S, Archararit N, Dahlan W, Puchaiwatananon O, Angtharak S, et al. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor-alpha and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *J Int Med Res*. 2004;32(5):443–54.
- Kremer JM, Lawrence DA, Jubiz W, DiGiacomo R, Rynes R, Bartholomew LE, et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunologic effects. *Arthritis Rheum*. 1990;33(6):810–20.
- Galarraga B, Ho M, Youssef HM, Hill A, McMahon H, Hall C, et al. Cod liver oil (n-3 fatty acids) as a non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology (Oxford)*. 2008;47(5):665–9.
- Adam O, Beringer C, Kless T, Lemmen C, Adam A, Wiseman M, et al. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatol Int*. 2003;23(1):27–36.
- Jorgensen KT, Pedersen BV, Jacobsen S, Biggar RJ, Frisch M. National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and pre-eclampsia? *Ann Rheum Dis*. 2010;69(2):358–63.

22. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012;367(6):495-507.
23. Cleland LG, Caughey GE, James MJ, Proudman SM. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. *J Rheumatol.* 2006;33(10):1973-9.

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