

Philadelphia College of Osteopathic Medicine DigitalCommons@PCOM

PCOM Physician Assistant Studies Student
Scholarship

Student Dissertations, Theses and Papers

2014

Is the Addition of Omega-3 Fatty Acids to Other Treatment Methods Effective in Reducing Pain in Adult Patients With Osteoarthritis?

Lisa C. Martin

Philadelphia College of Osteopathic Medicine, lisamart@pcom.edu

Follow this and additional works at: http://digitalcommons.pcom.edu/pa_systematic_reviews

 Part of the [Musculoskeletal Diseases Commons](#)

Recommended Citation

Martin, Lisa C., "Is the Addition of Omega-3 Fatty Acids to Other Treatment Methods Effective in Reducing Pain in Adult Patients With Osteoarthritis?" (2014). *PCOM Physician Assistant Studies Student Scholarship*. 203.
http://digitalcommons.pcom.edu/pa_systematic_reviews/203

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

**Is the Addition of Omega-3 Fatty Acids to Other Treatment Methods Effective in Reducing
Pain in Adult Patients with Osteoarthritis?**

Lisa C. Martin, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for
The Degree of Master of Science
In
Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

Objective: Is the addition of Omega-3 fatty acids to other treatment methods effective in reducing pain in adult patients with osteoarthritis?

Study design: Review of three published, double blind, randomized controlled trials were used for this review and were selected based on their relevance to the clinical question.

Data source: The most recent randomized control trials examining the relief of osteoarthritic pain with intake of omega-3 fatty acids in addition to traditional medical therapies were found using Medline, PubMed, and OVID databases.

Outcome measured: Relief of osteoarthritic pain with the addition of omega-3 fatty acids to the patients' normal therapy was the outcome measured. Attention was also paid to the occurrence of reported adverse events in all three studies.

Results: Gruenwald et al. demonstrated that the addition of omega-3 fatty acids to glucosamine sulfate was significantly superior to the use of glucosamine sulfate alone in reducing pain by 90-100% (n= 26 vs 12, respectively; $P_{\text{chi}}= 0.014$). Jacquet et al. demonstrated that the addition of omega-3 fatty acids, in the form of Phytalgic, to regular NSAID and analgesic use significantly reduced osteoarthritic pain (86.5) when compared to regular NSAID and analgesic use alone (235.3) assessed by WOMAC pain scores after three months of therapy with a p-value <0.001. Stammers et al. discovered no significant pain relief in patients taking 786mg eicosapentaenoic acid, in the form of cod liver oil, in addition to regular NSAIDs compared to patients taking a placebo (olive oil) in addition to regular NSAIDs after assessment with a t-test.

Conclusions: Although inconclusive, the results of these three randomized controlled trials demonstrates that the addition of omega-3 fatty acids to regular treatment modalities for relieving osteoarthritic pain is effective and deserves further investigation.

Key words: osteoarthritis, omega-3 fatty acids, fish oil

INTRODUCTION

Osteoarthritis (OA), a degenerative joint disease, is managed with a wide range of treatment strategies from acetaminophen to joint replacements. Omega-3 fatty acids are not encouraged as an approved treatment for OA despite the growing evidence of the herbal supplement's ability to decrease inflammation in disease states such as hyperlipidemia, rheumatoid and juvenile arthritis.¹ This paper will examine the results of three double blind, randomized clinical trials that explore the efficacy of using omega-3 fatty acids to relieve osteoarthritic pain.

OA is the most common chronic musculoskeletal disease with higher frequency in obese individuals, females, and those aged over 60 years. There are an estimated 21.4 million older Americans living with OA in 2005 which is expected to increase to 41.1 million by 2030.² OA affects 13.9% of adults older than 25 years and 33.6% of adults older than 65 years (12.4 million people over 65 years).³ Prevalence is predicted to rise by 66-100% by 2020 due to the increase in age and obesity.⁴

Annual cost is estimated at 7.9 billion dollars due to knee or hip OA replacement surgeries in 2009⁵ which translates to approximately \$36.5K per person during a 90 day period around a total joint replacement surgery⁶. Total annual out of pocket expenses have been estimated to cost Americans \$3,000 with total costs estimated at \$5,700 annually.⁷ OA was the primary diagnosis for 735,087 hospitalizations (1.9% of all discharges) in 2006⁸ and 7.1 million ambulatory visits (0.7%) in 1997⁹.

OA is an extensively studied disease due to its widespread prevalence and disability. OA is a joint degenerative disease marked by cartilage loss and osteophyte formation due to a

cytokine-driven inflammatory response which commonly affects the knees, cervical and lumbar spine, hips, and first metatarsal phalangeal joint. While much is known about the mechanism of disease, clinical features and risk factors, researchers have not found a cure nor has a widely successful non-invasive therapy been accepted to definitively treat OA. As previously mentioned, therapeutic management for OA ranges widely. Non-pharmacologic therapy includes patient education, physical therapy, occupational therapy, correction of malalignment, and unloading the joint through weight loss, bracing, shoe inserts, or activity modification. The gold standard pharmacologic therapy is acetaminophen 1.6-4g/d PO, although topical and oral non-steroidal anti-inflammatory drugs are also used. Narcotics (tramadol, opioids), serotonin and norepinephrine reuptake inhibitors (duloxetine) have been found to be beneficial and approved in treating osteoarthritic pain in conditional cases.^{10, 11} Corticosteroid (triamcinolone) or Na⁺ hyaluronic acid injections have been found to be effective in managing osteoarthritic pain. Some cases require surgery which includes osteotomy to fix malalignment, or partial/total joint replacement surgeries. Surgical joint replacements act as the most definitive therapy to treat OA to date. Prevention therapies include weight loss, correct leg length discrepancy, vitamin D supplements, chondroitin sulfate, glucosamine, hyaluronic acid. Omega-3 fatty acids have been shown to decrease inflammatory markers (IL-6 and TNF α) in juvenile arthritis¹ and inhibit inflammatory mediators (eicosanoids and cytokines) to aid in the treatment of rheumatoid arthritis and cardiovascular disease¹². Because cytokines and other inflammatory biomarkers contribute to the osteophyte formation in OA disease pathogenesis, it can be assumed that the anti-inflammatory abilities of omega-3 fatty acids may aid in the treatment of OA. The objective of this selective EBM review is to determine whether or not the addition of omega-3 fatty acids to other treatment methods is effective in reducing pain in adult patients with OA.

METHODS

This review focused on adults with OA. The intervention studied was the addition of omega-3-fatty acids to current medical therapy. Gruenwald et al. studied pain relief with glucosamine sulfate 500mg alone against an experimental group taking glucosamine sulfate 500mg with omega-3-fatty acids.¹³ Jacquet et al. compared pain relief with usual NSAID/analgesic use with a placebo to an experimental group taking usual NSAID/analgesic in addition to Phytagic, a supplement containing omega-3 FA.¹⁴ Stammers et al. compared pain relief with usual NSAID use with 10ml olive oil to an experimental group taking NSAIDs in addition to cod liver oil which contains EPA, an ingredient of omega-3 FA.¹⁵ Though many outcomes were measured in each study, the one outcome of concern was pain relief. The three studies were double blind randomized control clinical trials (RCT). Inclusion criteria included recent RCTs examining the effects of treating osteoarthritic pain with omega-3 fatty acids in addition to other medications in adults with OA. Exclusion criteria included patients younger than 25 years. Databases accessed to search articles included Medline, PubMed, and OVID and keywords included osteoarthritis, omega-3 fatty acids and fish oil. Each article was published in peer-reviewed journals and written in English. Statistical data analysis included the U-test, Mann-Whitney U-test, Chi-squared test, and repeated measures with confidence intervals (CI) set at 95% and p-value significance set at 5% in the study by Gruenwald et al.; t-tests, U-tests, Chi-squared, and Fischer tests with a CI set at 95% and p-value significance set at 5% in the study by Jacquet et al.; t-test and Mann-Whitney U-test in the study by Stammers et al.

Table 1: Demographics and characteristics of included studies

Article	Type of Study	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
2009 Gruenwald J, Petzold E, Busch R, Petzold HP, Graubau m HJ	2-center, 2-armed, randomized, double blind, comparison study	177 knee /hip OA	62.3	40-75yo, untreated OA sx, mod-severe hip or knee OA (WOMAC pain score= 300-400), limited function of hip or knee	Systemic dz, kidney/liver/GI dz; steroidal or non-steroidal anti-rheumatic, analgesics; allergy to ingredients; gamma-linolenic acid, glucosamine +/- chondroitin, alcohol, meds, drugs; HIV, AIDS, pregnant	1	1.5g glucosamine sulfate vs. 1.5g glucosamine sulfate + 600mg omega-3 FA x 26wks
2009 Jacquet A, Girodet PO, Pariente A, Forest K, Mallet L, Moore N	Randomized, double blind, parallel-arms clinical trial	81 knee /hip OA	57.1	40-80yo, chronic knee/hip OA evidenced by hx & X-ray evidence, taking NSAIDS &/or analgesics	Pregnant or lactating, shorter life expectancy than trial duration, inflammatory arthritis, OA not affecting knees or hips, allergy to product ingredients	5	Placebo + usual NSAID/analgesics vs. Phytalgic (fish oil, vitamin E, Urtica dioica)- in addition to pts usual NSAID/analgesics x 12wks
1992 Stammers T, Sibbald B, Freeling P	Double blind, placebo controlled randomized clinical trial	86 OA pts	68	49-87yo, pain associated with OA even while taking NSAIDS 2wks prior to start of trial	N/A	22	10ml olive oil + NSAIDS vs. 10ml cod liver oil (756mg EPA) + NSAIDS x 24wks

OUTCOMES MEASURED

Perception of pain caused by OA was measured by a standardized pain scale called the Western Ontario and McMaster Universities Arthrosis (WOMAC) in the first two studies^{13, 14} and by a visual analog scale (VAS) from 1-10 in the third study¹⁵. Gruenwald et al. also studied pain relief determined via VAS.¹³ Other outcomes measured were efficacy and safety perceived by the patient and practitioner, unwanted effects or harm perceived by the patient and assessed by the practitioner, activity limitations and disability perceived by the patient, and joint pain & inflammation assessed by the doctor. The latter outcomes were not evaluated in this study.

RESULTS

Efficacy of Results

All three RCTs explored the effect of adding omega-3 fatty acids to regular use of other treatment modalities in relieving osteoarthritic pain. The studies differed in measurement of pain, omega-3 fatty acid product used and comparison therapy. Gruenwald et al. examined the effects of adding 600 mg omega-3 fatty acids to 1.5 g glucosamine sulfate against 1.5 g glucosamine sulfate with an oil mixture containing all the same ingredients except EPA and DHA in reducing hip and knee osteoarthritic pain over 26 weeks in 177 patients.¹³ This study used the Western Ontario and McMaster Universities Arthrosis (WOMAC) scale to assess pain relief as well as a VAS measuring the patient's perception of pain intensity. The main results from this study showed that the addition of omega-3 fatty acids to glucosamine sulfate was significantly superior in pain relief when compared to using glucosamine sulfate with a placebo oil. While no significant difference was observed between the control and experimental group in reducing pain by less than 80%, significantly more patients who took omega-3 fatty acids with glucosamine

sulfate, experienced more than 90% pain reduction (n= 26) when compared to those who took glucosamine sulfate with placebo (n= 12) ($P_{\text{chi}}= 0.014$). Pain reduction measured via VAS from baseline to the end of the study showed that the experimental group experienced more pain reduction than the control group, although these results were not significant. The second study by Jacquet et al. examined the effects of omega-3 fatty acids in the form of Phytalgic, a medical food, against a placebo each with the addition of regular use of NSAIDs.¹⁴ This study used the WOMAC scale to assess hip and knee osteoarthritic pain relief in 86 subjects. The main results from this study showed significant OA pain reduction after taking omega-3 fatty acids in combination with regular NSAID and analgesic use (86.5) when compared to regular NSAID and analgesic use alone (235.3) assessed by WOMAC pain scores after three months of therapy (p-value <0.001). The third study by Stammers et al. examined the effects of adding 756 mg EPA, a component of omega-3 fatty acid, in cod liver oil against a placebo, olive oil, to the patients' regular use of NSAIDs.¹⁵ This study used a VAS to assess OA pain relief at 6 intervals during a 24 week period in 86 patients. This study demonstrated no significant pain relief in patients taking 786 mg eicosapentaenoic acid, in the form of cod liver oil, in addition to regular NSAIDs compared to patients taking a placebo (olive oil) in addition to regular NSAIDs after assessment with a t-test.

Treatment effects

In the study by Gruenwald et al., four patients in the control group experienced more than 90% pain reduction from baseline whereas 13 patients in the experimental group experienced more than 90% pain reduction from baseline. This equates to a control event rate (CER) of 5% and an experimental event rate (EER) of 14%, which yields a relative benefit increase (RBI) of 1.8 or 180% and an absolute benefit increase (ABI) of 0.09. Using RBI, the numbers needed to

treat (NNT) was calculated to be 11.1, meaning a health care provider needs to treat 12 adult patients with hip or knee osteoarthritic pain with adding omega-3 fatty acids to 500 mg glucosamine sulfate to have one additional patient experience more than 90% pain reduction. Twenty one patients experienced adverse effects, 12 from the experimental group and nine from the control group showing no significant difference. This yields a CER of 10% and an EER of 13%. The reported adverse events varied from mild to strong but none were considered serious. The relative risk increase (RRI) was calculated to be 0.291 or 29% and the absolute risk increase (ARI) was 0.03 or 3%. Numbers needed to harm (NNH) was calculated to be 33 from the equation $1/ARI$, meaning for every 33 patients treated with the addition of omega-3 fatty acids to glucosamine sulfate, one patient would experience an adverse event. Two subsets of each group was reported on. The full case analysis set (FAS) included 177 patients and the valid case analysis set (VCAS) included 164 subjects who met the full inclusion and compliance standards throughout the study. Both the FAS and VCAS groups were significant in pain reduction by more than 90% in the experimental group compared to the control in this study.

In the second and third study, there was no dichotomous data in which to report NNT so only NNH was calculated. In the study by Jacquet et al., 13 of the 40 patients in the control group and 14 out of the 41 patients in the experimental group experienced adverse effects, giving a CER of 32% and an EER of 34%.¹⁴ Although adverse events ranged from pain to infection, to pregnancy, only digestive adverse events were attributed to the experimental drug (flatulence, diarrhea, fish smelling eructations). The RRI was calculated to be 0.063 or 6% and the ARI was calculated to be 0.02 or 2%. The NNH was found to be 50, meaning for every 50 patients treated with omega-3 fatty acids in the form of Phytalgic in addition to NSAIDs and analgesics, one

patient would experience an adverse event. Two patients were withdrawn from the study, one from each group which did not alter the results.

In the study by Stammers et al., 23 total patients reported adverse effects of treatment, 10 in the control group (24%) and 13 (30%) in the experimental group.¹⁵ The adverse events varied from gastrointestinal complaints to dry skin, although no discernible relationship was found. RRI was calculated to be 25% and the ARI was 6%. NNH was found to be 17, meaning for every 17 patients treated with omega-3 fatty acids, in the form of cod liver oil, in the addition to regular NSAID and analgesic use, one patient would experience an adverse event. Twenty two patients failed to complete the study, 13 in the experimental group and nine in the control group without a comment in the article on how this drop-out rate influenced the results.

Table 2: Treatment effects

Study	RBI	ABI	NNT	RRI	ARI	NNH
Gruenwald et al	180%	0.09	12	29%	3%	33
Jacquet et al	N/A	N/A	N/A	6%	2%	50
Stammers et al	N/A	N/A	N/A	25%	6%	17

DISCUSSION

This systematic review demonstrates a possible aid in osteoarthritic pain relief by adding omega-3 fatty acids to other treatment modalities. Two of the three studies revealed pain relief after the addition of omega-3 fatty acids, however many questions remain unanswered and limitations of each study must be discussed. Due to the wide variation in both the control and experimental group therapies used in the current articles, it is difficult to estimate the exact role and efficacy of omega-3 fatty acids in treatment of osteoarthritic pain. Gruenwald et al. looked at the addition of 600 mg omega-3 fatty acids to 1.5 g glucosamine sulfate in comparison to 1.5 g glucosamine sulfate and placebo oil mixture.¹³ Both oils contained vitamin A, D and E with the presence of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) being the only difference in the oils. The amount of omega-3 oil as well as glucosamine sulfate was set at the above amount with compliance met if the patients took between 75% and 125% of this specified amount. The second study used Phytalgic in the intervention group which is a medical food consisting of omega-3 fatty acids, omega-6 fatty acids, *Urtica dioica* (a common nettle), zinc and vitamin E against a placebo which contained all the same except for a lack of omega-3 fatty acids and omega-6 fatty acids.¹⁴ Studying the effects of the omega-3 component alone is impossible as *Urtica dioica* has been found to have an analgesic effect, zinc has been found to decrease inflammation. Also in the exclusion of both omega-3 fatty acids and omega-6 fatty acids from the placebo, it becomes difficult to determine which component is the one that can be associated with the outcome of the study. Also of importance, the amount of omega-3 fatty acids was not specified (the article only specified the patients took 3 capsules) and the amount of analgesics and NSAIDs are varied because part of the objective of the study was to examine if there was a decrease in the regular voluntary use of analgesics or NSAIDs when taking

Phytalgic. Furthermore, omega-6 fatty acids have been associated with initiating inflammation.¹⁶

The third study differs in that it uses 10 ml cod liver oil which contains 756 mg EPA in comparison to a placebo of 10 ml olive oil. Olive oil contains over 30 polyphenols, some of which have anti-inflammatory properties¹⁷ and have been found to aid in pain treatment of rheumatoid arthritis suggesting it may be beneficial in treating OA pain. Use of other medications varied widely between opioids, NSAIDs and analgesics although the researchers set a specified dose of each drug.

While all three studies were double blinded to avoid bias, it may be assumed that it is well understood that “fishy burps” are a common side effect of omega-3 fatty acids (fish oil) supplements and therefore, patients taking experimental omega-3 fatty acid products with “fishy burps” may have biased response to pain if they are predisposed to their treatment modality. The study by Jacquet et al. took this fact into consideration when they found no change in their results when they excluded the two patients that complained of fishy burps.¹⁴

All studies were funded by groups with competing interests. The study by Gruenwald et al. and the study by Stammers et al. were funded by Seven Seas Limited, Hull UK. The study by Jacquet et al. was funded by Laboratoires Phythea.

CONCLUSION

Although further studies are warranted, after reviewing these three studies, the addition of Omega-3 fatty acids to other therapy is efficacious in the treatment of osteoarthritic joint pain. In all three studies a greater sample size with more control of “other treatment modalities” and a more targeted population would be beneficial to answering more targeted questions regarding the efficacy of omega-3 fatty acids on treating osteoarthritic pain. More targeted questions could aim at the effect of omega-3 fatty acids on osteoarthritic pain in specific joints or in males as compared to females or in combination with specified “other medications”. As outlined above, the treatment modalities of the studies differed greatly affecting the ease at which the studies and their results could be compared. Future studies should concentrate on standardizing the amount of DHA and EPA while eliminating the other substances that could potentially influence the inflammation disease process of OA which will help identify the role of omega-3 fatty acid in relieving OA pain. Standardizing the control group to a defined type and amount of “other treatment modality” would also help confine the results to reflecting the influence of the addition of omega-3 fatty acids. Because of the many joints affected in OA, it may be useful to separate the joints in future studies because of the weight bearing effects on inflammation. Future research should focus on the treatment of omega-3 fatty acids in relieving osteoarthritic pain in weight bearing joints such as the lower extremity (knees and hips) or lumbar spine as opposed to the non-weight bearing joints of the upper extremities as the weight bearing joints may exhibit more inflammation.

REFERENCES

1. Gheita T, Kamel S, Helmy N. Omega-3 fatty acids in juvenile idiopathic arthritis: effect on cytokines (IL-1 and TNF- α), disease activity and response criteria. *Clin Rheumatol*. 2012;31:363-366
2. Nho SJ, Kymes SM, Callaghan JJ, Felson DT. The burden of hip osteoarthritis in the United States: epidemiologic and economic considerations. *J Am Acad Orthop Surg*. 2013; 21(1):S1-6. doi: 10.5435/JAAOS-21-07-S1.
3. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. *Arthritis Rheum*. 2008; 58:26–35
4. Felson DT. Chapter 332. Osteoarthritis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?aID=9139147>. Accessed September 24, 2013.
5. Lethbridge-Cejku M, Helmick CG, Popovic FR. Hospitalizations for arthritis and other rheumatic conditions: Data from the 1976 national hospital discharge. *Medi Care*. 2003;41(12):1367-1373.
6. Bozic KJ, Stacey B, Berger A, Sadosky A, Oster G. Resource utilization and costs before and after total joint arthroplasty. *BMC Health Serv Res*. 2012;12:73.
7. Maetzel A, Li LC, Pencharz J, Tonlinson F, Bombardier C., The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension, a comparative study. *Ann Rheum Dis*. 2004;63(4):395-401.
8. Agency for Healthcare Research and Quality (AHRQ) HCUPNet. Accessed: Feb 8, 2009. Available at <http://hcupnet.ahrq.gov/HCUPnet.jsp?Id=27CD594BF07CA7D3&Form=DispTab&JS=Y&Acti>.
9. Hootman JM, Helmick CG, Schappert S. Magnitude and characteristics of arthritis and other rheumatic conditions on ambulatory medical care visits, United States, 1997. *Arthritis Care Res*. 2002;47(6):571-581.
10. Brown JP, Boulay LJ. Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee. *Ther Adv Musculoskeletal Dis*. 2013;5(6):291-304.
11. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465-74.
12. James M, Proudman S, Cleland L. Fish oil and rheumatoid arthritis: past, present and future. *Proceedings of the Nutrition Society*. 2010;69(3):316–323.
13. Gruenwald J, Petzold E, Busch R, Petzold HP, Graubaum HJ. Effect of glucosamine sulfate with or without omega-3 fatty acids in patients with osteoarthritis. *Adv Ther*. 2009;26(9):858-871.
14. 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.

15. 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.
16. Wardhana, Surachmanto EE, Datau EA. The role of omega-3 fatty acids contained in olive oil on chronic inflammation. *Acta Med Indones-Indones J Intern Med.* 2011;43(2):138-143.
17. Cardeno A, Sanchez-Hidalgo M, Alarcon-de-la-Lastra C. An update of olive oil phenols in inflammation and cancer: molecular mechanisms and clinical implications. *Curr Med Chem.* 2013;20(37):4758-76.