

# **Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids**

## **Arthritis & Rheumatism Volume 46, Issue 6, 2002, pgs. 1544-1553**

Clare L. Curtis, Sarah G. Rees, Chris B. Little, Carl R. Flannery, Clare E. Hughes, Chris Wilson, Colin M. Dent, Ivan G. Otterness, John L. Harwood, Bruce Caterson  
FROM ABSTRACT

### Objective

To determine if n-3 polyunsaturated fatty acid (PUFA) supplementation (versus treatment with n-6 polyunsaturated or other fatty acid supplements) affects the metabolism of osteoarthritic (OA) cartilage.

### Methods

The metabolic profile of human OA cartilage was determined at the time of harvest and after 24-hour exposure to n-3 PUFAs or other classes of fatty acids, followed by explant culture for 4 days in the presence or absence of interleukin-1 (IL-1).

Parameters measured were glycosaminoglycan release, aggrecanase and matrix metalloproteinase (MMP) activity, and the levels of expression of messenger RNA (mRNA) for mediators of inflammation, aggrecanases, MMPs, and their natural tissue inhibitors (tissue inhibitors of metalloproteinases [TIMPs]).

### Results

Supplementation with n-3 PUFA (but not other fatty acids) reduced, in a dose-dependent manner, the endogenous and IL-1-induced release of proteoglycan metabolites from articular cartilage explants and specifically abolished endogenous aggrecanase and collagenase proteolytic activity.

Similarly, expression of mRNA for ADAMTS-4, MMP-13, and MMP-3 was also specifically abolished with n-3 PUFA supplementation.

In addition, n-3 PUFA supplementation abolished the expression of mRNA for mediators of inflammation (cyclooxygenase 2, 5-lipoxygenase, 5-lipoxygenase-activating protein, tumor necrosis factor, IL-1, and IL-1) without affecting the expression of message for several other proteins involved in normal tissue homeostasis.

### Conclusion

These studies show that the pathologic indicators manifested in human OA cartilage can be significantly altered by exposure of the cartilage to n-3 PUFA, but not to other classes of fatty acids.

## THESE AUTHORS ALSO NOTE:

Loss of proteoglycan (aggrecan) from cartilage initiates degenerative joint disease.

The main enzymes responsible for the degradation of aggrecan are termed the aggrecanases.

Aggrecanase activity is increased by exposure of cartilage to proinflammatory substances.

Exposure of cartilage to mediators of inflammation contribute to the perpetuation and progression of arthritis.

These inflammatory mediators include eicosanoids (prostaglandins, leukotrienes, and thromboxanes) mediated through the cyclooxygenases (COX-1 and COX-2) and the lipoxygenase (LOX) isoform 5-LOX. **[IMPORTANT]**

COX is the enzyme that catalyzes the biosynthesis of prostaglandins and thromboxanes.

COX-2 activity is observed in human osteoarthritic (OA) cartilage and in synovial tissue from patients with rheumatoid arthritis.

The lipoxygenases enzyme LOX-5 is responsible for leukotriene biosynthesis.

Leukotrienes have a variety of proinflammatory effects, and increased levels have been implicated in a number of inflammatory diseases including arthritis.

“Clinical studies on dietary supplementation with n-3 (omega-3) polyunsaturated fatty acids (PUFAs), such as those present in fish oils, have demonstrated modulation of inflammatory symptoms involved in the pathogenesis of arthritis .”

Supplementation with n-3 PUFAs can elicit anti-inflammatory effects by decreasing leukotriene B4 levels, indicating an inhibition of the 5-LOX pathway, which is responsible for producing inflammatory leukotrienes from arachidonic acid.

N-3 PUFAs (but not other classes of fatty acids) causes an abrogation of cytokine-induced inflammation mediators and degradative enzymes.

“Fatty acid concentrations used in the study were levels that are achievable in human serum and are physiologically relevant.”

## RESULTS

“N-3 PUFA supplementation (18:3 [ $\alpha$ -linolenate] or 20:5 [eicosapentaenoate]) resulted in a dose-dependent decrease in GAG release,” which was statistically significant.

"In contrast, supplementation with n-6 PUFAs did not alter GAG release at any of the concentrations tested."

"Supplementation with oleic acid (monounsaturated) or palmitic acid (saturated fatty acid) had no effect on GAG release (data not shown)."

"Aggrecanase activity was abolished in control cultures that had been treated with n-3 PUFAs."

"In contrast, cultures pretreated with n-6 PUFAs showed no change in aggrecanase activity."

The expression of mRNA for the inflammation mediators COX-2, 5-LOX, and TNF was nearly abolished in cultures supplemented with n-3 PUFAs.

"N-6 PUFAs caused no change in the expression of mRNA for these inflammation mediators."

"Following n-3 PUFA supplementation, expression of mRNA for COX-2, IL-1, 5-LOX, was barely detectable."

## DISCUSSION

"The results of this study indicate that exposure of cartilage explants to n-3 fatty acids (but not other classes of fatty acids) can abrogate the pathologic indicators manifested by human osteoarthritic cartilage."

Human OA cartilage expresses modulators of inflammation (COX-2, 5-LOX, IL-1, TNF) and joint destruction."

"All of the disease markers present in the OA articular cartilage could be abrogated or reduced by culture for 24 hours with n-3 PUFAs."

N-3 PUFAs plays a role in halting or slowing degradative and inflammatory factors that contribute to the progression of OA. **[IMPORTANT]**

"Dietary supplementation with n-3 PUFA may prove useful in both quiescent and active arthritis." **[IMPORTANT]**

"Collectively, these findings suggest that n-3 PUFAs are involved in a metabolic coupling mechanism causing the suppression of expression of the degradative enzymes as well as the cytokines and inflammation factors that induce and propagate their expression in cartilage metabolism."

"Our findings support the results of epidemiologic and clinical studies that have demonstrated dietary supplementation with n-3 PUFAs to be beneficial in reducing pain and inflammation in human arthritic diseases." **[IMPORTANT]**

The occurrence of aggrecanase activity could be completely abolished when the diseased cartilage was incubated with n-3 PUFAs for 24 hours.

"This abolition of message and aggrecanase activity did not occur when the human OA cartilage explants were preincubated with n-6 or other classes of fatty acid."

"It is well recognized that polyunsaturated fatty acids can play a key role in the progression or prevention of human diseases by affecting either cellular membrane lipid composition, metabolism, or signal transduction pathways or by direct control of gene expression in a number of different tissues and cell types." **[WOW!]**

"It has long been recognized that dietary supplementation with fish oils that are enriched with n-3 PUFAs can provide benefit in the treatment of arthritis." **[WOW!]**

"Our findings indicate that n-3 PUFA supplementation can inhibit several pathophysiologic pathways in the diseased tissue [human OA]."

#### KEY POINTS FROM DAN MURPHY

(1) Various pro-inflammatory eicosanoids are derived enzymatically from arachidonic acid (a omega-6 fatty acid), and they contribute to the degradative processes that lead to osteoarthritis.

(2) Omega-3 PUFAs are anti-inflammatory, and they halt or slow the degradative and inflammatory factors that contribute to osteoarthritis.

(3) Omega-3 PUFAs reduce the pain and inflammation in human arthritic diseases.

(4) Dietary supplementation with n-3 PUFA is useful in both quiescent and active arthritis.

I get my omega-3 oils from Sears Lab, because they are pharmaceutical grade (mercury free and fewer than 10 ppb PCBs), I can take them in mega-doses for my bad back (I take 10 grams per day) without poisoning myself, and I can take a liquid form (2 tablespoons is 10 grams) rather than 20 capsules.

We have also seen numerous articles on how omega-3s help the cardiovascular system, helps with cardiac arrhythmias and prevents sudden cardiac death, helps the brain (in terms of development and neurodegenerative diseases), and helps the immune system (in terms of allergy, asthma, rheumatoid arthritis, etc.)

**Sears Lab Phone Number Is: 800-404-8171**