



Integrated pain management: using omega 3 fatty acids in a naturopathic model

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Pain management for patients with chronic pain is a difficult task for most physicians. Many pain centers are beginning to use an integrative approach to pain management by including naturopathic physicians on the patient's team. The foundation of naturopathic care is the therapeutic order of treatment. Initially, those factors that determine the foundation of health are addressed, such as diet, sleep, emotional wellness, and exercise. A naturopathic physician will then tailor treatment to the level of disease starting with less invasive treatments or those with lesser risk of toxicity, such as botanical medicine, clinical nutrients, and homeopathy. The next step on the therapeutic order is to correct structural integrity through acupuncture and manual therapies. Finally, natural and synthetic are applied to address hormonal, immunologic aspects of pain or for symptomatic relief. The highest force interventions include medications with greater risk of toxicity and surgical interventions.

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Case studies

An example of a successful integrated medicine strategy can be observed in Mike, a 55-year-old male with rheumatoid arthritis who was referred to a naturopathic physician for treatment to complement his conventional therapy. He was experiencing side effects from his conventional regimen and could not achieve adequate pain control with medication doses that allowed him to remain functional. The naturopathic physician reviewed his diet for potential adverse food reactions, reviewed his medications for nutrient depletions, and provided treatment to support his current medication regime by improving tolerance. One such treatment is oxytocin, a pain modulator that binds to opioid receptors and stimulates nitric oxide synthesis and has low toxicity and few drug interactions. He underwent a series of acupuncture treatments (8-10 weekly visits), and afterward he followed up one to two times per year with the ND and was referred back to the pain center and rheumatologist for monitoring. By combining conventional and naturopathic treatments, this patient experienced better control of his pain as well as stabilization of his disease process, which was not attainable by either conventional or naturopathic therapy alone.

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Ms. Jacobson is a 64 year old female with mild osteoarthritis in both knees. She presented to my office with a history of using various NSAIDs and acetaminophen to control her knee pain. However, she has significant gastric distress with taking NAIDs and acetaminophen does not provide adequate pain relief. She is active in her community and goes dancing with her husband twice weekly. She is also wanting to start a tai chi class but her knee pain is keeping her from enjoying these activities. After reviewing her prescription medications for potential interactions, I prescribed a fish oil concentrate that provided 1500 mg EPA. She noted decreased pain and increased functionality after six weeks and was able to maintain the fish oil without complication.

Omega 3 fatty acids fall into dietary as well as clinical nutrient therapy, depending on the source and amount prescribed. Omega 3 fatty acids (n-3) play a pivotal role in regulating both acute and chronic inflammation, which is generally promoted by omega 6 fatty acids (n-6). However, the Western diet is severely deficient in n-3 fatty acids. A high n-6:n-3 diet creates a predisposition to chronic inflammation and alters the resolution of acute inflammation.

Fatty acids and diet

Arachidonic acid is maintained at high cellular concentrations by the high n-6 and low n-3 polyunsaturated fatty acid

content of the modern Western diet. Human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of approximately 1:1, whereas in Western diets, the ratio is 15:1 to 16.7:1.¹

Metabolism of fatty acids

Alpha-linolenic acid (ALA, 18:3 n-3) and linoleic acid (LA, 18:2 n-6) are essential fatty acids. They cannot be synthesized in the body as double bonds can only be inserted into the carboxyl end (Δ), not the methyl end (ω) of fatty acids. Thus, n-9 fatty acids, such as oleic acid, cannot be used to create n-3 or n-6 fatty acids. Likewise, n-3 and n-6 fatty acids cannot be interchanged in the body.

Alpha linolenic (n-3) and linoleic acid (n-6) are the starting points of the metabolic chain events for the n-3 and n-6 pathways, respectively (Figures 1 and 2). Both pathways share three desaturase enzymes, although n-3 fatty acids appear to have metabolic precedence, being the preferred fatty acid for prostaglandin synthesis. However, dietary preponderance of n-6 to n-3 can lead to competitive saturation of the desaturase enzymes, resulting in a predominance of n-6 end products, namely arachidonic acid. Thus, the beneficial effects of omega-3 fatty acids are reduced when the diet is high in omega-6 fatty acids.²

Omega-6 fatty acids are a key component in cell signaling necessary for the inflammatory process. Inflammatory

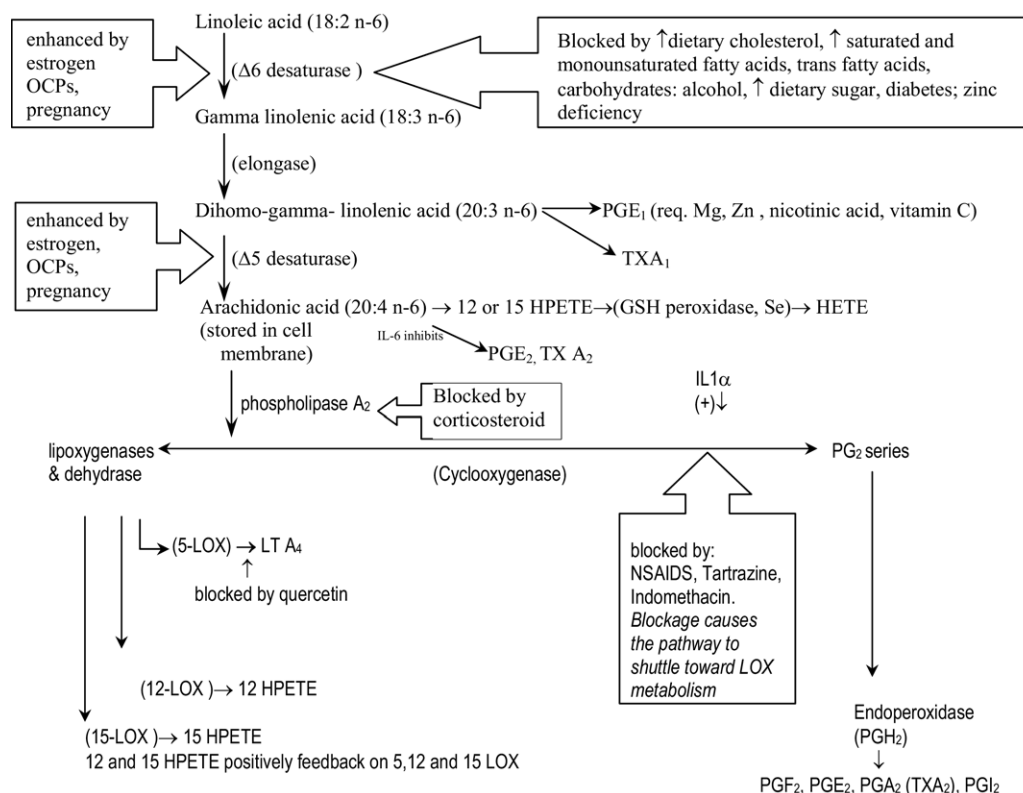


Figure 1 n-6 pathway.

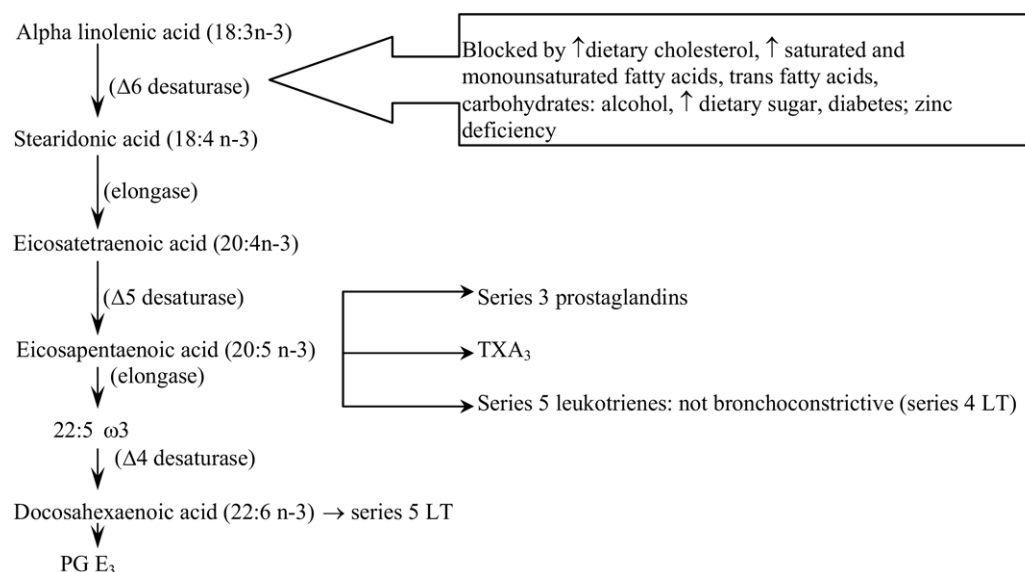


Figure 2 n-3 pathway.

mediators arise from the alteration of the n-6 fatty acid arachidonic acid (AA) Through cyclooxygenase and lipoxygenases, AA is converted to proinflammatory eicosanoids including prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄) (Figure 1). In turn, n-3 fatty acids can decrease the chronic inflammatory response through the production of antiinflammatory eicosanoids, including PG I₂ and PGE₁ (Figure 2). EPA can act as a competitive inhibitor of AA conversion to PGE₂ and LTB₄, and decreased synthesis of one or both of these eicosanoids has been observed after inclusion of n-3 fatty acids in the diet.

Flaxseed oil contains the ALA, which can be converted after ingestion to eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3). Fish oils contain both EPA and DHA. Bioconversion of ALA to EPA and DHA is slow and inefficient, however. In adult men, conversion to EPA is approximately 8% and conversion to DHA is extremely low (<0.1%). In women, fractional conversion to DHA appears to be greater (9%), theoretically due to the up-regulation of the conversion of EPA to DHA by the stimulation of estrogen on one of the desaturase enzymes.³

Fatty acids and cell signaling

Diets rich in n-3 fatty acids are associated with suppression of cell-mediated immune responses. N-3 fatty acids from fish oil supplementation can inhibit the expression of MHC class II and adhesion molecules on monocytes present within chronically inflamed joints, as well as circulating activated monocytes, and reduce the ability of activated monocytes to present antigen to autologous lymphocytes.⁴

Regarding the proinflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-1β, studies of healthy volunteers and rheumatoid arthritis patients have shown 40% to 90% inhibition of cytokine production after

dietary supplementation with fish oil.⁵ Several studies have shown that supplementation of the diet of healthy volunteers results in reduced ex vivo production of IL-1, IL-6, TNF, and IL-2 by peripheral blood mononuclear cells. Animal studies indicate that dietary fish oil reduces the response to endotoxin and to pro-inflammatory cytokines, resulting in increased survival; such diets have been beneficial in some models of bacterial challenge, chronic inflammation, and auto-immunity.⁶ In vitro animal and ex vivo human studies have reported a decrease in mRNA and protein levels of a number of cytokines, including TNF-α, IFN-γ, IL-1, IL-2, and VCAM-1.⁷ In multiple sclerosis, supplementation with n-3 fatty acids decreased production of IL-1-β, TNF-α, IL-2, IFN-γ, prostaglandin E₂ (PGE₂), and LTB₄ in unstimulated and stimulated peripheral blood mononuclear cells in people with MS and healthy controls.⁸

One mechanism of action for n-3 fatty acids is believed to block formation of pro-inflammatory mediators through substrate competition.⁹ Recently, another role of n-3 fatty acids has been found; they are used to generate lipid mediators that are agonists in antiinflammation during the course of inflammation and its active resolution.

Omega 3 fatty acids in acute inflammation

Neutrophils are able to congregate swiftly in large numbers in acute inflammation. During this process, they inadvertently release noxious substances intended to kill or neutralize invaders, which can also damage local tissue damage. Specifically, neutrophils release mediators derived from the n-6 fatty acid arachidonic acid (AA). During the initial phase of inflammation, prostaglandins such as PGE₂ are generated, which are involved in the early steps of the control of blood flow and vessel dilation needed for leukocytes to undergo firm adhesion and diapedesis.¹⁰ Also,

LTB₄, a potent chemoattractant involved in the recruitment of additional neutrophils and leukocytes to the initial area of insult.¹¹ However, as the course of acute inflammation continues, mediators switch classes, which includes switching substrates from n-6 to n-3 fatty acids to form novel families of chemical mediators.¹² The resolution of acute inflammation specifically involves mobilization of different fatty acid precursors that appear within exudates, arachidonic acid, EPA, and DHA in a temporally orchestrated fashion. The n-3 fatty acid derivatives promote resolution of acute inflammation by shortening the time interval of the return of involved tissue to homeostasis.

Clinical application of omega 3 fatty acids and dietary therapy

The beneficial effects of dietary n-3 fatty acids may be of use as a therapy for acute and chronic inflammation and for disorders which involve an inappropriately activated immune response. An antiinflammatory diet should consist of a relatively high consumption of cold water fish, high oleic oils (olive, peanut, almond, macadamia, and high heat varieties of canola oil), as well as a low intake of n-6 fats and arachidonic acid (red meat, dark meat poultry, shrimp). n-3 fatty acids should be consumed at approximately 40 mg/kg body weight/day, with dietary (n-6) fatty acid intake <10 g/day in the background diet, resulting in substantial cellular incorporation of (n-3) fatty acids and improvements in clinical status in patients with RA.¹³

Dosages of omega 3 fatty acids in studies generally show 1.5 g/day to be minimally effective. Doses tend to be higher in studies that show significant benefit in reducing clinical presentation in ankylosing spondylitis (4.55 g/day, 7 to 21 weeks),¹⁴ multiple sclerosis (6 g/day containing 3 g EPA and 1.8 g DHA for 6 months),⁸ and rheumatoid arthritis (4.5 g/day, monitored every 3 months).¹⁵ Using omega-3 fatty acids may seem like snake oil. However, keep in mind that Chinese snake oil contains 20% EPA.¹⁶

Naturopathic medicine is an important aspect of integrated pain management. However, be aware that not all practitioners claiming the title of ND, naturopathic doctor, or naturopathic physician are trained equally. Only refer to naturopathic physicians trained at naturopathic medical schools approved by the Council on Naturopathic Medical Education, which is recognized by the U.S. Dept. of Edu-

cation as the accrediting body for naturopathic programs (see <http://www.cnme.org>). The American Association of Naturopathic Physicians is also a good location tool for naturopathic physicians trained in CNME approved programs (<http://www.naturopathic.org>).

References

1. Simopoulos AP: Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. *Biomed Pharmacother* 60:502-507, 2006
2. Cleland LG, James MJ, Neumann MA, et al: Linoleate inhibits EPA incorporation from dietary fish-oil supplements in human subjects. *Am J Clin Nutr* 55:395-399, 1992
3. Williams CM, Burdge G: Long-chain n-3 PUFA: plant v. marine sources. *Proc Nutr Soc* 65:42-50, 2006
4. Hughes DA, Pinder AC: n-3 polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes. *Am J Clin Nutr* 71:357S-360S, 2000 (suppl)
5. James MJ, Gibson RA, Cleland LG: Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 71:343S-348S, 2000 (suppl)
6. Calder PC: n-3 polyunsaturated fatty acids and cytokine production in health and disease. *Ann Nutr Metab* 41:203-234, 1997
7. Calder PC: Dietary modification of inflammation with lipids. *Proc Nutr Soc* 61:345-358, 2002
8. Gallai V, Sarchielli P, Trequattrini A, et al: Cytokine secretion and eicosanoid production in the peripheral blood mononuclear cells of MS patients undergoing dietary supplementation with n-3 polyunsaturated fatty acids. *J Neuroimmunol* 56:143-153, 1995
9. Lands WEM (ed): Proceedings of the American Oil Chemists' Society Short Course on Polyunsaturated Fatty Acids and Eicosanoids. Champaign, IL, American Oil Chemists' Society, 1987
10. Pouliot M, Fiset ME, Masse M, et al: Adenosine up-regulates cyclooxygenase-2 in human granulocytes: impact on the balance of eicosanoid generation. *J Immunol* 169:5279-5286, 2002
11. Borgeat P, Samuelsson B: Arachidonic acid metabolism in polymorphonuclear leukocytes: effects of ionophore A23187. *Proc Natl Acad Sci U S A* 76:2148-2152, 1979
12. Bannenberg GL, Chiang N, Ariel A, et al: Molecular circuits of resolution: formation and actions of resolvins and protectins. *J Immunol* 174:4345-4355, 2005
13. Volker D, Fitzgerald P, Major G, et al: Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *J Rheumatol* 27:2343-2346, 2000
14. Sundström B, Stålnacke K, Hagfors L, et al: Supplementation of omega-3 fatty acids in patients with ankylosing spondylitis. *Scand J Rheumatol* 35:359-362, 2006
15. Cleland LG, Caughey GE, James MJ, et al: Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. *J Rheumatol* 33:1973-1979, 2006
16. Kunin RA. Snake oil. *West J Med* 151:208, 1989