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Pain

ω-3 Fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain†

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Abstract

Background: The use of NSAID medications is a well-established effective therapy for both acute and chronic nonspecific neck and back pain. Extreme complications, including gastric ulcers, bleeding, myocardial infarction, and even deaths, are associated with their use. An alternative treatment with fewer side effects that also reduces the inflammatory response and thereby reduces pain is believed to be ω-3 EFAs found in fish oil. We report our experience in a neurosurgical practice using fish oil supplements for pain relief.

Methods: From March to June 2004, 250 patients who had been seen by a neurosurgeon and were found to have nonsurgical neck or back pain were asked to take a total of 1200 mg per day of ω-3 EFAs (eicosapentaenoic acid and decosahexaenoic acid) found in fish oil supplements. A questionnaire was sent approximately 1 month after starting the supplement.

Results: Of the 250 patients, 125 returned the questionnaire at an average of 75 days on fish oil. Seventy-eight percent were taking 1200 mg and 22% were taking 2400 mg of EFAs. Fifty-nine percent discontinued to take their prescription NSAID medications for pain. Sixty percent stated that their overall pain was improved, and 60% stated that their joint pain had improved. Eighty percent stated they were satisfied with their improvement, and 88% stated they would continue to take the fish oil. There were no significant side effects reported.

Conclusions: Our results mirror other controlled studies that compared ibuprofen and ω-3 EFAs demonstrating equivalent effect in reducing arthritic pain. ω-3 EFA fish oil supplements appear to be a safer alternative to NSAIDs for treatment of nonsurgical neck or back pain in this selective group.

Keywords: Spine pain; ω-3 EFA; Nonsteroidal anti-inflammatory drugs

1. Introduction

In 1971, Vane [34,35] suggested that blockage of the COX enzyme would inhibit the conversion of arachidonic acid to the very proinflammatory PGs that mediate the classic inflammatory response of pain (dolor), edema (tumor), elevated temperature (calor) , and erythema (rubor). Since then, NSAIDs that block COX have been used for analgesia and anti-inflammation for a plethora of medical conditions. More than 70 million NSAID prescriptions are written each year, and 30 billion over-the-counter NSAID tablets are sold annually. It is estimated that 5% to 10% of the adult US population and approximately 14% of the elderly routinely use NSAIDs for pain control [9].

This multibillion dollar industry, however, does not come without risk. NSAID-associated dyspepsia occurs in up to 50% of users [29]. Almost all patients who take the long-term nonselective (inhibits both COX 1/COX 2) NSAIDs will demonstrate subepithelial gastric hemorrhage, and 8% to 20% more will have ulceration. In addition, 3% of patients

Abbreviations: ALA, α-Linolenic acid; COX, Cyclooxygenase; DHA, Decosahexaenoic acid; EPA, Eicosapentaenoic acid; EFA, Essential fatty acids; FDA, Food and Drug Administration; IL, Interleukins; LOX, Lipoxygenase; MI, Myocardial infarction; NSAIDs, Nonsteroidal anti-inflammatory drugs; PG, Prostaglandin.

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develop serious gastrointestinal side effects, which results in more than 100 000 hospitalizations, an estimated 16 500 deaths, and an annual cost to treat the complications that exceeds 1.5 billion dollars annually [21]. Indeed, NSAIDs are the most common cause of drug-related morbidity and mortality reported to the FDA and other regulatory agencies around the world. In a recent editorial, Roth [25] compared the chronic systemic use of NSAIDs to "carpet-bombing," with attendant collateral end-stage damage to human organs.

Recently, it was found that the COX 2 inhibitors, designed to alleviate the gastric side effects of COX 1 NSAIDs, are not only associated with an increased incidence of MI and stroke but also have no significant improvement in the prevention of gastric ulcers [4,8,24,30].

Having routinely prescribed NSAIDs for our patients with discogenic and arthritic pain for many years and aware of the NSAIDs' serious side affects, we reviewed nonpharmaceutical anti-inflammatory agents routinely prescribed by physicians practicing complimentary medicine for alternatives to NSAIDs. These included turmeric (*Curcuma longa*), the fragrant yellow spice found in curry and used for centuries in ayurvedic medicine, which has many of the same effects as aspirin without its anticoagulation properties [38]; boswellia, an extract from a tree in India whose acids have anti-inflammatory action very similar to that of NSAIDs [1]; bromelain, an enzyme contained in pineapple that also interferes with PG synthesis; white willow bark, a natural precursor to aspirin but without the unpleasant gastrointestinal side effects; and green tea, which is also a potent anti-inflammatory and antioxidant [10,18].

The agent best documented by hundreds of references in the literature for its anti-inflammatory effects is ω-3 EFAs found in fish and in pharmaceutical-grade fish oil supplements [5,23,27,28]. The active ingredients in polyunsaturated essential fatty acid are EPA and DHA that, once released by the injured cell membrane, can competitively inhibit the proinflammatory interleukins (IL-1, IL-6, and IL-12), tumor necrosis factor α, and the 2 series of inflammatory PGs [6]. There is extensive documentation in the rheumatology, ophthalmology, and cardiovascular literature on the beneficial anti-inflammatory affects of high-dose fish oil in the reduction of joint pain from rheumatoid and osteoarthritis, improvement in dry eyes and macular degeneration, and also major positive affects on lipid profile, plaque formation arrhythmias, and reduction in infarction from coronary arthrosclerosis, which is now considered an inflammatory disease [2,3,7,36].

With this background, we conducted the following study to evaluate the potential effectiveness of ω-3 EFA acid as an alternative for patients with discogenic and arthritic spine pain who were already taking NSAIDs for pain control.

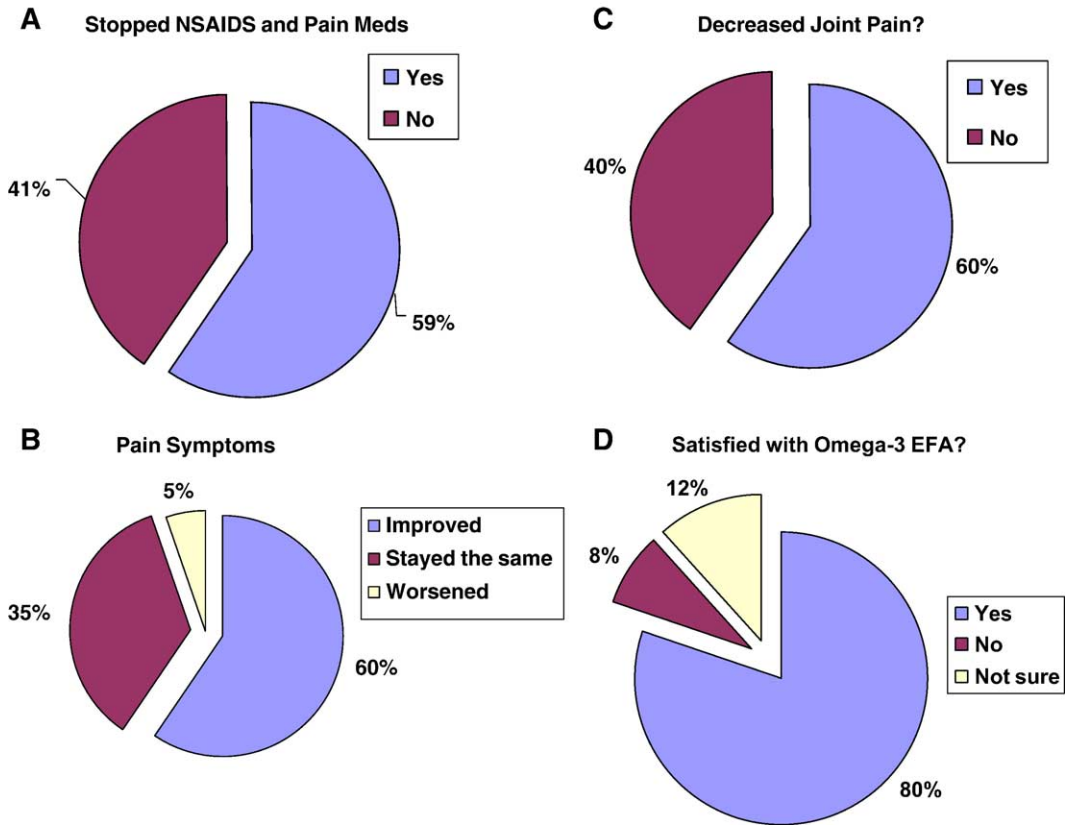

Fig. 1. A: Most patients stopped their NSAIDs and pain medicines after 2 months on fish oil. B: The majority had less pain symptoms—their experience when using fish oil. C: Joint pain improved in 60% of the respondents. D: Eighty percent were satisfied with fish oil.

2. Methods

From March 2004 to June 2004, 250 patients were evaluated for nonsurgical spine pain: the majority had degenerative disk disease with facet arthropathy in the lumbar and/or cervical spine. All were taking NSAIDs with 75% on COX 2 inhibitors. They were asked to take ω-3 EFAs (EPA and DHA) found in pharmaceutical-grade fish oil supplements at a dose of 2.4 g for 2 weeks then 1.2 g thereafter. After the initial 2 week period, they were instructed to taper off of their NSAIDs over 1 to 2 weeks. A questionnaire was then forwarded to these patients approximately 1 month after initially taking the supplement. The questionnaire asked for subjective clinical improvement of joint and spine pain, any side effects, and to what degree they were able to discontinue using their current NSAIDs.

3. Results

Of the 250 patients, 125 have returned the questionnaire at an average of 75 days on fish oil. Seventy-eight percent were taking the 1200 mg and 22%, 2400 mg of ω-3 EFAs in the form of EPA and DHA, and 59% reported to have discontinued taking any NSAID medication for pain (Fig. 1A). Sixty percent stated their overall pain was improved, as compared with before starting on ω-3 EFAs (Fig. 1B), and 60% stated specifically that their joint pain had improved (Fig. 1C). Eighty percent of the respondents stated they were satisfied with their improvement (Fig. 1D), and 88% stated they would continue to take the ω-3 EFA (fish oil). There were no significant side effects reported except for 2 patients who reported loose bowel movements on 1200 mg/d.

4. Discussion

Both natural and synthetic corticosteroids have powerful anti-inflammatory effects. They reduce the migration of white blood cells seen in inflammation, thus decreasing the production and action of the complement proteins, PGs, cytokines, and thromboxanes that induce inflammation [15,16]. They also have well-described side effects primarily related to decreased healing capabilities, decrease in the normal protective aspects of the immune response, and also significant bone and gastric side effects.

Because of these problems and others, a new class of NSAIDs was developed to reduce the side effects but continue the positive anti-inflammatory effects. The enzyme COX was found to be either a constitutive form (COX-1) or an inducible form (COX-2). NSAIDs block COX-1 and COX-2 selectively or jointly. This is significant because COX is a key enzyme that regulates PGE_2 synthesis, a proinflammatory cytokine [8,24].

Several authors have demonstrated the significance of the arachidonic acid pathway in the pain associated with discogenic disease [11,12,19,22,26,33]. Miyamoto et al [20] have shown immunohistologically that COX-2 is expressed in lumbar herniated disk specimens and produced PGE_2; furthermore, the selective inhibition of COX-2 inhibited this proinflammatory PGE_2 production [16].

The literature reviewing rheumatoid and osteoarthritis, both chronic inflammatory conditions, consistently report improvements in joint pain and function by using ω-3 EFA. Cleland [6] reported a 27% improvement in tender joint score, as compared with an 8% improvement with placebo for rheumatoid arthritis. Kremer [14] reported a 39% joint pain reduction along with a reduction in leukotriene B4, an inflammatory cytokine, in these same patients. And in 1995

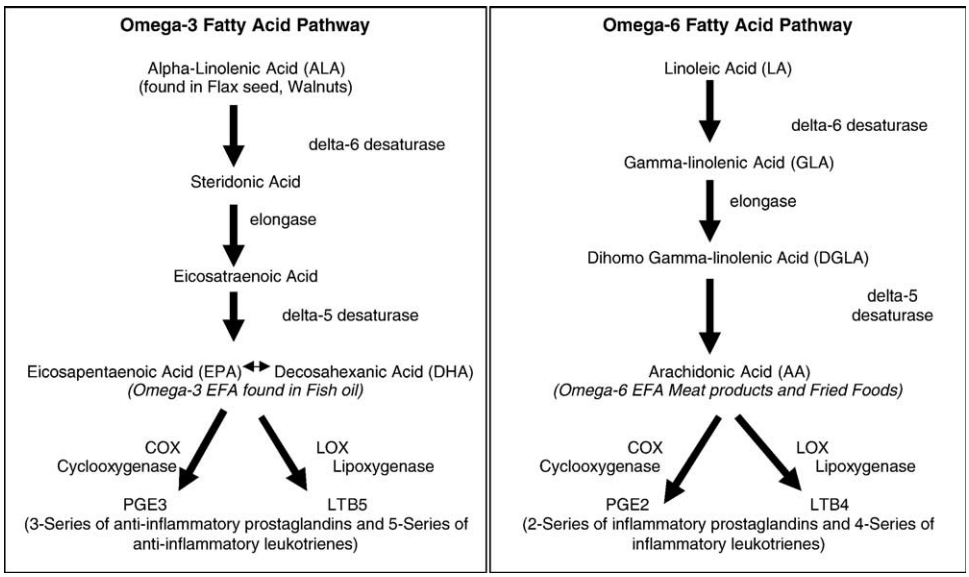

Fig. 2. These pathways both use COX and LOX as the enzymes for conversion. Thus, the more EPA from fish oil (ω-3 EFA), the less COX and LOX are available for the arachidonic path way.

[13], he reported another placebo-controlled study during which patients were slowly removed from the NSAID diclofenac over an 8-week period and were either substituted with ω-3 EFA (130 mg/kg per day) or corn oil (placebo), and the EFA group had significantly less joint pain at the end of the 8 weeks. Interestingly, Stammers et al [31,32] reported no significant adjunctive effects of EFA given with NSAIDs, and they concluded that the NSAIDs blocking the COX enzyme may also block the ω-3 pathway to the anti-inflammatory PGs. This conclusion is consistent with Fig. 2 showing how EPA requires the COX enzyme to form the group 3 PGs.

The use of both COX-1 and the more recent COX-2 inhibiting NSAIDs have been the mainstay for treatment of chronic spine pain as well as other conditions related to inflammation and has grown to more than 9 billion US dollars in annual sales [8,24]. The COX-2 inhibiting class was perceived to lack serious side effects, but this was significantly challenged when on September 30, 2004, the FDA acknowledged the voluntary withdrawal of Vioxx™ (rofecoxib), a COX-2 selective NSAID manufactured by Merck & Co. The concern for an increased risk of serious cardiovascular events, including MI and strokes, stemmed from a clinical trial to determine whether Vioxx could reduce the risk of colon cancer [4,30]. It became apparent that besides inhibiting COX-2, these agents selectively interfered with prostacyclin synthesis, a PG essential in reducing intravascular coagulation, thus the increased incidence of MI and stroke. Because of significant gastric and now cardiovascular side effects, there now appears to be limited pharmaceutical choices remaining to a health practitioner when treating chronic pain associated with inflammation [8,24]. In fact, a recent warning to physicians recommends consents similar to operative permits be obtained before prescribing NSAIDs [17] (Fig. 3).

Cox-2 Inhibitor Consent Form

Your medical provider has considered the use of Celebrex/other (circle one) as part of your care. Such "Cox-2 inhibitor" drugs appear to be associated with an increased risk of strokes and/or heart attacks, occurring in about 1-1.2% of individuals who take them for periods of about three years compared to 0.3% of patients taking only sugar pills. Traditional arthritis drugs such as naproxen/Aleve also appear to be associated with lesser but increased risks of stroke and heart attacks than previously recognized.

Cox-2 inhibitor drugs are no stronger for pain control than traditional arthritis medications like ibuprofen/Advil. While they are associated withless risk of stomach ulcers and bleeding, such problems can still occur.

In all other ways, Cox-2 inhibitors share the same risks of side effects as traditional arthritis medications.
My medical provider has reviewed this matter with me. I understand and accept such risks and I have asked my provider to prescribe this medication for me.

Date_____ Signature_____

Print name_____

Date_____ Signature _____

Print provider's name _____

Fig. 3. Sample COX-2 Inhibitor Consent Form, as it appeared in the Allegheny County Medical Bulletin, June 2005, page 296.

4.1. Alternative choice

Essential fatty acids linoleic acid and ALA are fats that we must consume in our diet. Fatty acids are characterized by the number of double bonds that are present in the molecule. Saturated fatty acids have no double bonds, monounsaturated have 1 double bond, and polyunsaturated fatty acids have 2 or more double bonds. The polyunsaturated fatty acids can be subdivided into 2 categories, ω-3 EFAs and ω-6 EFAs. The ω-3 EFAs (ALA) have their first double bond located at the third carbon position, whereas the ω-6 EFA (linoleic acid) have their first double bond at the sixth carbon. These EFAs are used to produce the phospholipids that are necessary for the formation and maintaining integrity of healthy cell membranes, neuronal development, and functioning of the brain and nervous system [28].

Corn oil, sunflower oil, and safflower oil contain linoleic acid, a ω-6 EFA. When consumed in large amounts, such is common in the Western diet, excessive linolenic acid leads to the formation of arachidonic acid, which then forms the proinflammatory PGE_2. Animal proteins, especially red meat, also contain an abundant amount of arachidonic acid. Eating lean meat such as turkey, chicken and fish, and lean cuts of beef and pork will limit the formation of arachidonic acid hence less PGE_2 is formed [28].

PGE_3 is also a PG but is derived from ω-3 EFAs, which are found primarily in fish and, to a lesser extent, flax seed, walnuts, and certain algae. A deficiency in ω-3 fatty acids, especially EPA and DHA, which are very bioactive, will result in a deficiency in PGE_3 and LT(leukotriene)D-5 both anti-inflammatory PGs.

EFAs are also required for the production of hormone-like substances called eicosanoids (thromboxanes, leukotrienes, and PGs). We know that eicosanoids regulate numerous body functions including blood pressure, blood viscosity, vasoconstriction, and immune and also the inflammatory response. EPA, DHA, and arachidonic acid are the most biochemically active products converted to eicosanoids. EPA and DHA are ω-3 EFAs found in the highest concentrations in fish oil. DHA and EPA are used to make the anti-inflammatory and less coagulogenic eicosanoids (PGE_1 and PGE_3), whereas excress ω-6 EFAs form inflammatory arachidonic acid based eicosanoids (PGE_2) (Fig. 4) [11,14,32].

Conversion of ω-6 EFAs is regulated by 2 important enzymes: δ-6 and δ-5 desaturase. δ-6 Desaturase converts linoleic acid to the metabolically active γ-linolenic acid, which can then be converted to prostacyclin, which has anti-inflammatory properties. δ-5 desaturase is used in this pathway to form arachidonic acid, which is then converted by COX to PGE_2 and by LOX to leukotriene 4, both powerful inflammatory PGs [28].

In general, a more favorable balance of PG production occurs in the ω-6 EFA pathway by allowing δ-6 desaturase activity and inhibiting δ-5 desaturase activity. Both δ-6 desaturase and δ-5 desaturase are also used in the ALA

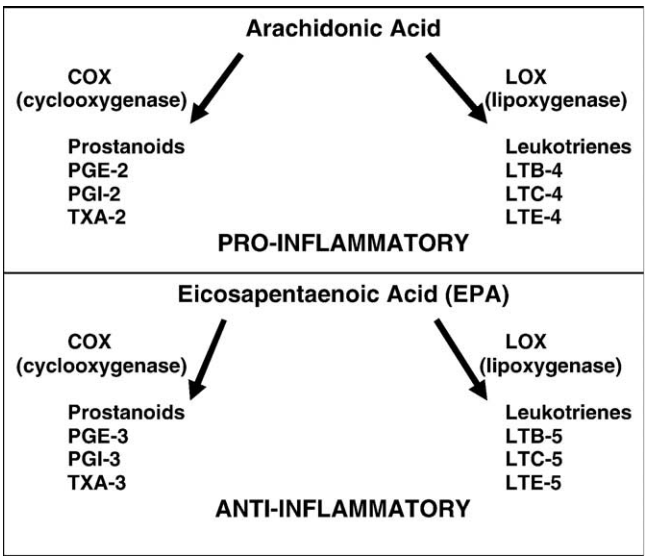

Fig. 4. The metabolic pathway for the conversion of ALA to PGE_3 the anti-inflammatory PGs. Metabolic pathway for the conversion of linoleic acid to PGE_2 the inflammatory PGs (right). The ω-3 fatty acid EPA, along with DHA, is found in high concentration in fish oil, and meat contains large amounts of arachidonic acids.

(a ω-3 fat) metabolic pathway to convert EPA, which is then converted by COX and LOX to PGE_3 and leukotriene 5, and other anti-inflammatory PGs [28].

Age inhibits δ-6 desaturase activity. After 30 years of age, the body's ability to convert EFAs to PGs diminishes. Diet also can inhibit δ-6 desaturase activity. A diet high in refined carbohydrates with subsequently elevated blood glucose slows δ-6 activity and decreases the production of PGs. Similarly a diet high in transfatty acids, alcohol consumption, stress, or a genetic defect that results in a lack of δ-6 desaturase will inhibit the function of this enzyme.

Because δ-5 desaturase converts γ-linolenic acid to arachidonic acid which is then converted to inflammatory PGs, δ-5 desaturase acts as a gatekeeper to inflammation and, therefore, ideally, must be controlled. Elevated insulin levels increases δ-5 desaturase activity and, as a result, persons with diabetes are prone to chronic inflammation, especially coronary artery disease. Thus, if the body has insufficient δ-6 desaturase activity or excessive δ-5 desaturase activity, both controlled by diet and age, adequate amounts of prostacyclin and PGE_3, which are anti-inflammatory, will not be produced [28]. Interestingly, δ-5 desaturase is not required to convert EPA found in cold water fish directly into anti-inflammatory PGs.

To encourage the production of anti-inflammatory PGs and to discourage the production of inflammatory PGs, saturated fats, transfatty acids, and arachidonic acid should be reduced in the diet; blood glucose should be controlled; and appropriate amounts of ω-3 fatty acids found in fish oils should be consumed.

The positive human clinical effects of ω-3 EFAs are now the subject of more than 900 scientific articles, with many showing that ω-3 EFA fish oil acts as a natural anti-inflammatory and, thus, a possible alternative choice to NSAIDs [36]. This research supports its safe and effective use for many inflammation-related conditions and its low incidence of side effects.

The conversion of EPA into anti-inflammatory PGs of the PGE_3 series is by the same COX enzyme used by arachidonic acid to convert to the proinflammatory PGs PGE_2 (Fig. 4) series; thus, by competitive inhibition, the higher level of EPA (DHA) one has, the more COX is shifted or consumed to make more of the anti-inflammatory PGs (Fig. 2). The simultaneous use of ω-3 EFAs and COX inhibitors slows this conversion to PGE_3 and, therefore, potentially reduces the benefit to the cells of the PGE_3 series anti-inflammatory PGs. Therefore, COX inhibitors can also inhibit the effectiveness of fish oil [34].

4.2. Dosage

The US Department of Agriculture has limited fish consumption to 1 fish serving per week in adults and even less in children and pregnant women because of the concern of toxic contaminants such as mercury, polychlorinated biphenyls, and dioxin in our fish population. For this reason, the most usable form of ω-3 EFA is fish oil supplements, which have been purified to remove any of these contaminants. For our evaluation, we have used 1200 mg of ω-3 EFA (EPA/DHA) per day. There is no known unsafe upper limit, but greater than 5 g/d of ω-3 EFA fish oil is not usually recommended. Eskimo diets have been reported to have up to 16 g of ω-3 EFAs per day, but blood studies did indicate prolonged bleeding times; therefore, it is recommended that if patients are on anticoagulants, close monitoring by a physician for possible alterations in coagulation status is important.

4.3. ω-3 Index

In 2004, Harris and von Schacky [37], developed the ω-3 index, which is a measurement of EPA/DHA in red blood cells as a measure of adequate or inadequate levels of ω-3 EFAs in the body. They then compared cardiac risk based on these levels and developed a risk assessment for coronary artery disease. This index is also useful for dosing ω-3 EFAs to determine the optimum levels of ingested ω-3 EFAs to obtain the appropriate amount of red blood cell saturation. With this test, which is a simple finger stick, the dose of ω-3 EFAs can be more accurately titrated and, thus, eliminate under or overdosing, which now appears to be common.

4.4. Side effects

Because this is a natural food supplement, side effects are very rare. Occasionally, at higher dosages, 5 g or more, or in some sensitive people, fish oil has been associated with stearrhea. In our evaluation of 250 patients, we had only 3 (2%) with this complaint. We did not recommend the fish oil for those on anticoagulants or fish-related allergies. Aspirin use was not a contraindication.

5. Conclusion

There are several weaknesses with this study. It is a retrospective, non–placebo-controlled survey that was intended to determine if patients could effectively substitute fish oil as an anti-inflammatory in place of NSAIDs. The placebo effect, the variability in underlying patient pathology, and the lack of long-term follow-up are all weaknesses to be addressed. Nevertheless, this may serve as a starting point to investigate the use of ω-3 EFAs as well as other nonpharmaceutical agents as treatment alternatives for spine-related pain. That close to two thirds of patients could discontinue NSAIDs is certainly provocative, especially given the recent FDA warnings regarding their complications. The effectiveness of ω-3 EFAs in rheumatoid and some cases of osteoarthritis has been demonstrated. Appropriately designed studies are needed to confirm the effectiveness of ω-3 EFA for pain relief in discogenic pain.

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