Omega-3 Fatty Acids for Neuropathic Pain
Case Series

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Objective: The aim of this case series study was to investigate and report on patients with neuropathic pain who responded to treatment with omega-3 fatty acids.

Methods: Methods: Five patients with different underlying diagnoses including cervical radiculopathy, thoracic outlet syndrome, fibromyalgia, carpal tunnel syndrome, burn injury were treated with high oral doses of omega 3 fish oil (varying from 2400-7200 mg/day of EPA-DHA). Outcome measures were obtained pretreatment and posttreatment. These included validated surveys (short-form McGill Pain questionnaire, DN4 neuropathic pain scale, Pain Detect Questionnaire), objective clinical tools (Jamar grip strength, Lafayette dynamometry, tender point algometry) and EMG Nerve Conduction studies.

Results: These patients had clinically significant pain reduction, improved function as documented with both subjective and objective outcome measures up to as much as 19 months after treatment initiation. No serious adverse effects were reported.

Conclusions: This first-ever reported case series suggests that omega-3 fatty acids may be of benefit in the management of patients with neuropathic pain. Further investigations with randomized controlled trials in a more specific neuropathic pain population would be warranted.

Key Words: neuropathic pain, ω-3 fatty acids, radiculopathy, carpal tunnel syndrome, fibromyalgia

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INTRODUCTION

Omega-3 Fatty Acids and Chronic Disease

Omega-3 (or *n*-3; ω-3) fatty acids (FAs) are long-chain polyunsaturated FAs of plant and animal origin, which are typically 18, 20, or 22 carbon atoms in chain length. The term "ω-3" signifies that the first double bond in the molecule is located at the third carbon position counting from the ω-end of the FA chain. Fish oil from oily fish is a rich source of long-chain ω-3 FAs, consisting mainly of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3).[1] Vegetable oils are not a source of EPA or DHA although certain types (eg, flaxseed and walnut oil) do contain varying amounts of an alternate form of ω-3 FA known as α-linolenic acid (ALA; 18:3n-3).[2,3] ALA can be metabolized by the body into the longer chain EPA and DHA through a series of desaturation or elongation reactions.[3]

The benefits of ω-3 FA supplementation are well documented in the literature for the prevention and management of a wide variety of health conditions including inflammatory joint pain,[4–6] chronic spinal pain,[7] autoimmune diseases,[8,9] cardiovascular disease,[3,10,11] and depression. Ozgocmen et al investigated the effect of ω-3 FAs in the management of fibromyalgia syndrome in an open, noncontrolled single-blind study involving 12 female patients.[12] The patients were treated for a period of 4 weeks with high doses of ω-3 FAs. Results from the study showed statistically significant beneficial changes from the baseline for, tender point counts, chest expansion measurements, and pain severity, fatigue, and depression scales, using the Fibromyalgia Impact Questionnaire.

Omega-3 Fatty Acids and Neuropathic Pain

To date there are no clinical trials that have examined the effects of ω-3 FA supplementation in the treatment of neuropathic pain (NeP) patients. Moreover, very few studies have investigated the mechanisms whereby ω-3 FAs may modulate NeP. There are considerable differences between chronic NeP and chronic inflammatory pain. The eicosanoid-dependent anti-inflammatory effects of ω-3 FAs may not be relevant to NeP conditions. A significant factor in NeP is the activation in the spinal cord of non-neural glial cells, macroglia, and astrocytes.[13] Activated glia are characterized by proliferation, hypertrophy, and increased production of inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. EPA and DHA could possibly reduce the production of these cytokines but this remains to be determined.[4] In this regard, it is noteworthy that DHA has recently been shown to play a larger role in neurogenic inflammation than previously anticipated.[14,15]

It has been suggested that ω-3 FAs may block pain neuron voltage-gated sodium channels (VGSCs) that underlie NeP.[16] The gene encoding 1 of the nociceptor specific VGSCs, SNS/PN3, shares a very similar genomic structure with the human cardiac VGSC gene. Omega-3 FAs are known to potently and reversibly bind to and block current through

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this cardiac VGSC.[16] Outside of their neurologic influences, some evidence suggests a role for ω-3 FAs in the modulation of the stress response through influence of plasma cortisol. Low-plasma cortisol, which is required to blunt the inflammatory process and therefore influence the inflammatory component of NeP is associated with essential FA deficiencies.[17]

CASE SERIES

We now present the case series of NeP patients who improved with the use of ω-3 FA supplements. This case series is the first ever published on using ω-3 FA supplements in the treatment of NeP. Updated criteria in diagnosis such as the DN4 and Pain Detect Questionnaires (PDQ) were used.

Patient 1: C7 Radiculopathy

A 53-year-old left-handed police officer was seen for right-sided cervical radiculopathy. He had developed neck symptoms in 2004. His symptoms worsened to the point by December 2005 where he could no longer play hockey and had sleeping problems. Magnetic resonance imaging results showed evidence of a C6/C7 right lateral disk herniation compressing of the right C7 nerve root with spinal stenosis and mutilevel degenerative disk disease. Past-medical history included anxiety or panic attacks, depression, gout, and vasectomy.

Earlier treatments included: physiotherapy, naproxen, and other nonsteroidal anti-inflammatory drugs such as ibuprofen (Advil). His other medications included diltiazem, omeprazole (Losec), enteric-coated acetylsalicylic acid, and co-codamol (Tylenol-3).

Physical examination, in July 2006, revealed a height of 186 cm with a weight of 104 kg. Blood pressure (BP) was 106/77 mm Hg. Biomechanical examination revealed a marked head forward posture with tight pectorals and poor core stability. Neurologic examination (Table 1) revealed a weak right triceps with possible right rotator cuff impairment and vasculogenic thoracic outlet compression, which also would perpetuate symptoms. In addition, he had a positive right Allen test and weakness in the C6/C7 myotomes.

The patient was started on a treatment of high doses of ω-3 FAs (8 capsules/d totaling 4800 mg EPA/DHA). After two and half weeks his pain started to subside. He was reassessed in March 2007 after taking ω-3 FAs for a little over eight months. Strength measurements were done and his triceps strength on the right side was now greater than on the left (Table 1). Jamar grip strength was also improved. His short-form McGill pain questionnaire (SF-MPQ) rating decreased to 0/45 and he started playing hockey and working out again.

The patient returned in February 2008 and was still benefiting from the ω-3 FAs (Table 1). His Numeric Rating Scale (NRS) pain score was 0/10. Weight and BP were unchanged. He cited a time when he forgot to bring his ω-3 FAs to a hockey tournament and noted recurrence of neck pain after 4 days. Otherwise, he continues to be pain free and able to play full equipment ice hockey.

Patient 2: Thoracic Outlet Syndrome

A 48-year-old right-handed registered nurse, married mother of 2, was referred for left lateral epicondylalgia. Her work, in the continuing care department of the hospital, involves the transfer of heavy patients. She injured her left arm while transferring a 111 kg patient. After the injury, she was not able to cut the grass or shovel snow. With help, she could perform some household chores including vacuuming. Symptoms were aggravated by activity and alleviated by rest. Past-medical history included a work-related injury to the low back in August 2005 and neck pain because of a whiplash injury.

Earlier treatments included physiotherapy, which ameliorated symptoms, and meloxicam (Mobicox). She took calcium carbonate and vitamin D supplements daily.

Her physical exam revealed a height of 165 cm with a weight of 56.7 kg. BP was 123/76 mm Hg. She had regional myofascial pain with spread involvement proximally into the shoulder girdle and down into the hand. Some degree of thoracic outlet compression was also noted with positive Allen test, often brought on with head forward posture and tight scalene and pectoral muscles. She had 14/18 fibromyalgia tender points. Before taking ω-3 FAs, her SF-MPQ rating was 7/45 (Table 2) with mild use of emotional descriptors. Pain at its worst was rated at 8/10.

She was started on a treatment of ω-3 FAs (4 capsules/d totaling 2400 mg EPA/DHA). After taking ω-3 FAs for 7 months her epicondylitis pain was much improved, although she still reported burning pain when she would

TABLE 1. Patient 1 Physical Exam Before and After ω-3 FA Treatment

	Initial Assessment	8 Months After Treatment	19 Months After Treatment
EMG-nerve conduction studies	Normal motor and sensory studies of the right median and ulnar nerves. Needle exam revealed chronic denervation potentials with decreased recruitment in the right C7 innervated triceps and flexor digitorum superficialis muscles	Needle exam revealed marked improvement in recruitment in C7 muscles	—
Lafayette manual muscle test of arm extension (triceps)	Right: 29.5 kg, left: 54.4 kg	Right: 56.7 kg, left: 55.8 kg	Right: 56.7 kg, left: 56.7 kg
Jamar grip strength	Right: 12.7 kg, left: 18.1 kg	Right: 18.1 kg, left: 19.1 kg	—
SF-MPQ score	30/45	0/45	4/45

Following the initial assessment and prescription of ω-3 FAs, follow-up examinations were done after 8 months and after 19 months of treatment.
EMG indicates electromyography; FA, fatty acids; SF-MPQ, short-form McGill pain questionnaire.

TABLE 2. Patient 2 Physical Exam Before and After ω-3 FA Treatment

	Initial Assessment	7 Months After Treatment	13 Months After Treatment
Jamar grip strength	Right: 22.7 kg, left: 11.3 kg	Right: 25.0 kg, left: 18.1 kg	—
PDQ score	20/35	—	6/35
DN4 score	5/10	—	1/10
SF-MPQ score	7/45	4/45	—

Following the initial assessment and prescription of ω-3 FAs, follow-up examinations were done after 7 months and after 13 months of treatment.
FA indicates fatty acids; PDQ, Pain Detect Questionnaire; SF-MPQ, short-form McGill pain questionnaire.

exert her elbow. She did not require cortisone injections. Her Jamar grip improved (Table 2) and fibromyalgia tender points decreased to 9/18. Overall pain was reported lower at 2/10 with a best of 0/10 and worst 4/10. Her SF-MPQ score was 4/45. After 13 months, her PDQ and DN4 scores decreased considerably (Table 2).

Patient 3: Cervical Radiculopathy

A 50-year-old right-handed Holter monitor company representative was diagnosed with chronic right C7 radiculopathy. In 2003, he was involved in a motor vehicle accident. Magnetic resonance imaging results revealed evidence of right central disk protrusion at C6/C7. There was also evidence of severe spinal stenosis at C5/C6 and moderate stenosis at C4/C5 and C6/C7. He reported limitations in such areas as, self-care, household responsibilities, social activity, recreation, sports, grip, lifting from floor to waist, and lifting overhead.

Past treatments included physiotherapy, chiropractic treatment, massage therapy, and occasional nonsteroidal anti-inflammatory drugs. He also supplemented with B-vitamins and coenzyme-Q10.

Physical exam revealed a height of 181 cm with a weight of 109 kg. BP was 142/95 mm Hg. He showed evidence, both electrodiagnostically (moderately prolonged median sensory and motor latencies, 2+ denervation in C7 myotomes) and on clinical exam, of weakness in the right arm. His average pain was reported at 6/10 with a best of 0/10 and worst 9/10. Jamar grip strength as well as SF-MPQ, PDQ and DN4 scores before ω-3 FA supplementation are reported in Table 3.

The patient was started on a treatment of high doses of ω-3 FAs (8 capsules/d totaling 4800 mg EPA/DHA; he later increased his dosage to 10 to 12 capsules/d totaling 7200 mg EPA/DHA). He later reported no pain during activity and was able to actively work out at the gym. He also reported of sharper brain function and feeling clear-headed. After taking ω-3 FAs for 17 months, his SF-MPQ, PDQ, and DN4 scores decreased and his Jamar grip improved (Table 3).

Patient 4: Carpal Tunnel Syndrome

A 47-year-old right-handed self-employed auto mechanic presented with a 2 and half-month history of pain, numbness, and cramping in his right hand. Symptoms were worse with repeated gripping. He had no neck or proximal pain. Past-medical history included kidney stones, a motor vehicle accident whiplash injury 15 years before consultation, sports injuries in high school (concussion), and right palm laceration at the age 10 without any long-term neurologic sequelae. He was a nonsmoker and did not drink alcohol. Family history included a father with diabetes, colon cancer, and heart disease.

Physical exam in January 2008, revealed a height of 171 cm with a weight of 108 kg (heavy-set build). Biomechanical examination revealed a 3+ head forward posture with anterior protracted shoulders. Thoracic outlet syndrome and neural tension tests were negative. Tinel test was negative and Phalen test was positive. Abductor pollicis brevis strength was measured at grade 4+. Jamar and lateral key pinch were above average (Table 4). No sensory loss or hyperesthesia was noted. Left rotator cuff tendonitis (impingement pain) was noted. Electrodiagnostic examinations showed a marked, prolonged right median motor distal latency, and right median sensory latencies (Table 4).

The patient was started on a treatment of ω-3 FAs (5 capsules/d totaling 3000 mg EPA/DHA). When reassessed in September 2008, after approximately 8 months of treatment, his global symptom score for carpal tunnel syndrome decreased and electrodiagnostic examinations showed marked improvements (Table 4). He improved to the point where surgery was not needed. He continued with fulltime work and was very pleased with the effects of the ω-3 FAs.

Patient 5: Worker Compensation Burn Injury

A 54-year-old right-handed restaurant worker fell down stairs with a vat of hot oil and sustained 30% total body surface area burns (second and third degree; Fig. 1). He was stabilized in the local hospital and then transferred to Sunnybrook Health Sciences Centre (trauma burn unit). He was hospitalized in the burn unit for 40 days and underwent extensive skin grafting and debridement procedures.

TABLE 3. Patient 3 Physical Exam Before and After ω-3 FA Treatment.

	Initial Assessment	17 Months After Treatment
Jamar grip strength	Right: 59.0 kg, left: 65.7 kg	Right: 63.5 kg, left: 65.7 kg
PDQ score	10/35	1/35
DN4 score	4/10	0/10
SF-MPQ score	17/45	6/45

Following the initial assessment and prescription of ω-3 FAs, a follow-up examination was done after 17 months of treatment.
FA indicates fatty acids; PDQ, Pain Detect Questionnaire; SF-MPQ, short-form McGill pain questionnaire.

TABLE 4. Patient 4 Physical Exam Before and After ω-3 FA Treatment.

	Initial Assessment	9 Months After Treatment	14 Months After Treatment
EMG-nerve conduction studies	Median nerve conduction studies: motor distal latency; right: 5.0 ms, left: 3.7 ms (normal is < 4.1 ms). Motor amplitude; right: 6.1 mV, left: 10.3 mV. Conduction velocity: 51 m/s (normal is > 50 m/s). Sensory latency (digit 2/3); right: 4.1/4.1 ms, left: 2.7/3.0 ms (normal is < 2.6 ms). Conduction velocity (digit 2/3); right: 32/32 m/s, left: 49/45 m/s. Ulnar studies and needle EMG exam were normal	Median nerve conduction studies: motor distal latency; right: 4.4 ms, left: 3.5 ms (normal is < 4.1 ms). Motor amplitude; right: 8.7 mV, left: 10.3 mV. Conduction velocity: 52.3 m/s (normal is > 50 m/s). Sensory latency (digit 2/3); right: 3.2/3.3 ms, left: 2.9/3.0 ms (normal is < 2.6 ms). Conduction velocity (digit 2/3); right: 41/41 m/s, left: 48/46 m/s	—
Jamar lateral key pinch	Right: 8.2 kg, left: 8.2 kg	Right: 11.6 kg, left: 12.3 kg	—
Global symptom score	22/50	13/50	13/50

Following the initial assessment and prescription of ω-3 FAs, follow-up examinations were done after 9 months and after 14 months of treatment. EMG indicates electromyography; FA, fatty acids.

When he was transferred to the rehabilitation hospital in March 2006, he was taking morphine 10 mg up to 9 days. Despite extensive multidisciplinary management, including physiotherapy, occupational therapy, nursing, psychologic counseling, and massage therapy, he still had severe burning pain (DN4 criteria was 7/10 with burning, electric shocks, tingling, pins and needles, numbness, pinprick, and light touch hypoesthesia). His NRS pain score and Neuropathy Pain Scale (NPS) were 8/10 and 85/100, respectively.

The patient was transitioned to long-acting morphine (MS Contin). Pregabalin (Lyrica) was added at 25 mg qam and 75 mg qhs. Bupropion (Wellbutrin) was introduced and helped with mood. NRS pain score improved to 6/10 and NPS to 68/100. In May 2006, ω-3 FAs were added and titrated up to 2 capsules for every 23 kg of body weight. When reassessed after 4 months, there were objective improvements in goniometric range of motion of the shoulder and neck. The NRS pain score was 4.5/10 and the NPS further improved to 32/100.

The patient transitioned successfully to outpatient care and subsequent vocational retraining. He was able to wean down the morphine and found the high dose of ω-3 to be most beneficial.

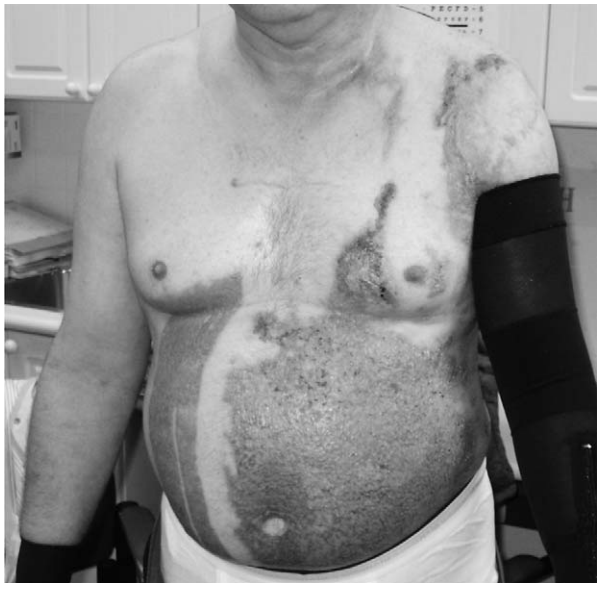

FIGURE 1. Second and third degree burns sustained by patient 5.

DISCUSSION

Before prescribing ω-3 FAs or any other nutraceutical, it is important to do a full medical work-up to rule out a more serious pathology (cancer, infection, aneurysm, etc). One must get a full list of medications and over-the-counter products used by patients. Important interactions with the use of ω-3 include effects on coagulation. For example, if patients are on Coumadin, then a more gradual titration of ω-3 and frequent checking of the international normalized ratio would be advisable. If patients are diabetic, then the addition of ω-3 will increase caloric intake and patients are advised to adjust their diet and insulin accordingly (long-term use of ω-3, however, does reduce insulin resistance and improves diabetic control).

Because of the "blood-thinning" effects of ω-3 FAs, we usually advise patients to discontinue their use 2 weeks before any surgery, dental work, or invasive procedures (eg, colonoscopy). Herbal products such as ginkgo, curcumin, and ginger should also be discontinued.

Laboratory analyses should be performed to monitor patients on high dose ω-3. This includes markers of "silent inflammation" and includes the arachidonic acid (AA) to EPA (AA:EPA) ratio. The average North American ratio is 12:1. An optimal ratio for cardiovascular health is 1.5 to 3:1. Excess intake of ω-3, which translates into a ratio of 0.5:1, is associated with an increased risk for hemorrhagic stroke. Unfortunately, such laboratory testing is expensive and most of our patients did not undergo such testing unless they were taking extremely high doses of 7500 mg EPA/DHA or more per day. Testing is available at laboratories such as Nutrasource Diagnostics, Inc (Guelph, Ontario, Canada). This laboratory measures the serum phospholipid levels, which is more accurate, and more studied, than red blood cell levels. Other useful laboratory tests to detect silent inflammation include the high

sensitivity C-reactive protein (optimal levels are < 1.0), fasting insulin (optimal level is < 10 uIU/mL), and triglyceride to high-density lipoprotein ratio (optimal level is < 2). The references and research for this are summarized in chapters 4 and 7 of the book: Anti-inflammation Zone by Barry Sears, PhD.[18]

It is important to recommend a high-quality brand of ω-3. Patients are taught to read labels and ensure that products have been tested for impurities and have good potency. A product with a higher concentration of EPA/DHA per serving is advisable over a similar product with a lower concentration of EPA/DHA. With regards to purity, websites such as the www.ifosprogram.com will list ω-3 products that have been independently lab tested for contaminants such as heavy metals (including mercury), polychlorinated biphenyls, and dioxin. The standards set by IFOS for ultra-refined EPA/DHA concentrate are very rigorous with upper limits set as follows: mercury < 10 parts per billion, polychlorinated biphenyls < 45 parts per billion, dioxins < 1 part per trillion, and total oxidation < 13 mEq/L.

A recommended conservative dose is 2700 mg of EPA and DHA, on the basis of the Goldberg and Katz meta-analysis.[4] However, a more aggressive approach for more severe pain can be up to 7500 mg of EPA and DHA. The latter approach will require serum laboratory tests to monitor the AA:EPA ratio.

For patients who experience stomach difficulties or nausea from the use of ω-3 FAs, we usually advise them to try freezing the capsules. A better response occurs with enteric-coated capsules. Digestion is improved when ω-3 FAs are taken with food. It is also useful to split the dosage between several meals instead of ingesting the supplements all at once.

Patients should clearly be instructed to take only ω-3 and not ω-3 to 6 to 9. The ω-6 FAs are proinflammatory and the use of such products will not help in relieving pain.[19] Omega-6 FAs are essential, but in the typical North American diet, excess is already ingested.[19]

It should be noted that ω-3 FAs are just 1 component of an overall integrative medical approach in treating pain and optimizing wellness. Patients must learn to improve their diets and reduce their intake of AA commonly found in red meat and fried foods. Furthermore, diets that are deficient in vitamin B6, magnesium, zinc, and have excessive trans-FAs [7] and caffeine lead to impaired δ-6 desaturase activity that is required in the pathway that converts ALA to EPA. We often combine ω-3 FAs and other nutraceuticals with judicious courses of anti-inflammatory drugs, such as celecoxib,[20] for postsurgical and postmusculoskeletal trauma. For severe NeP (NRS pain > 6/10), we combine ω-3 with pregabalin. For comorbid depression, w-3 can be combined with duloxetine or tramadol. For opioid-resistant NeP, pharmaceutical cannabinoids are also helpful (nabilone, Sativex spray).

Long-lasting lifestyle changes need to be adopted to ensure long-term relief of pain. This includes appropriate exercise, both cardiovascular and core strengthening, weight-loss, stress reduction (prayer, meditation, humor), and good sleep hygiene. Efforts to detoxify the body of unhealthy "toxic" substances, such as trans-fats, and unhealthy "talk-sick" attitudes and behaviors are all important.

To conclude, the use of ω-3 FA supplements for the treatment of NeP shows promise, on the basis of these case studies. Further research in the way of randomized double-blind placebo-controlled trials would be needed to validate the use of ω-3 FAs for NeP. We hope this article will stimulate such research and lead to greater pain-free wellness in our patients.

REFERENCES

1. Cleland LG, James MJ, Proudman SM. Fish oil: what the prescriber needs to know. *Arthritis Res Ther*. 2006;8:202.
2. Logan AC. Neurobehavioral aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Altern Med Rev*. 2003;8:410–425.
3. Holub DJ, Holub BJ. Omega-3 fatty acids from fish oils and cardiovascular disease. *Mol Cell Biochem*. 2004;263:217–225.
4. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain*. 2007;129:210–223.
5. Calder PC. Polyunsaturated fatty acids and inflammation. *Prostaglandins Leukot Essent Fatty Acids*. 2006;75:197–202.
6. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006;83(6 suppl): 1505S–1519S.
7. Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. *Surg Neurol*. 2006;65:326–331.
8. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr*. 2002;21:495–505.
9. Calder PC. Immunomodulation by omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids*. 2007;77:327–335.
10. Jenkins DJ, Josse AR, Beyene J, et al. Fish-oil supplementation in patients with implantable cardioverter defibrillators: a meta-analysis. *CMAJ*. 2008;178:157–164.
11. Lee JH, O'Keefe JH, Lavie CJ, et.al. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc*. 2008;83:324–332.
12. Ozgocmen S, Catal SA, Ardicoglu O, et al. Effect of omega-3 fatty acids in the management of fibromyalgia syndrome. *Int J Clin Pharmacol Ther*. 2000;38:362–363.
13. White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of neuropathic pain. *Proc Natl Acad Sci USA*. 2007;104:20151–20158.
14. Orr SK, Bazinet RP. DHA playing an unexpected role in neurogenic inflammation. *Curr Opin Investig Drugs*. 2008;9: 735–743.
15. Vedin I, Cederholm T, Freund Levi Y, et al. Effects of docosahexaenoic acid-rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes: the OmegAD study. *Am J Clin Nutr*. 2008;87:1616–1622.
16. Shapiro H. Could n-3 polyunsaturated fatty acids reduce pathological pain by direct actions on the nervous system? *Prostaglandins Leukot Essent Fatty Acids*. 2003;68:219–224.
17. Bistrian BR, Bothe A Jr, Blackburn GL, et al. Low plasma cortisol and hematologic abnormalities associated with essential fatty acid deficiency in man. *JPEN J Parenter Enteral Nutr*. 1981;5:141–144.
18. Sears B. *The anti-inflammation zone*: *reversing the silent epidemic that's destroying our health*. New York, New York: Harper-Collins; 2005.
19. Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr*. 1999;70(3 suppl):560S–569S.
20. Adhami VM, Malik A, Zaman N, et al. Combined inhibitory effects of green tea polyphenols and selective cyclooxygenase-2 inhibitors on the growth of human prostate cancer cells both in vitro and in vivo. *Clin Cancer Res*. 2007;13:1611–1619.