NestléHealthScience

Considerations for Nutritional Products containing Fish Oil

Background

The use of fish oil in nutritional formula first took place in the United States over 20 years ago with the introduction of IMPACT® Formula, and the use of high omega-3 containing oils in many other health care nutrition products has followed.

Fish oil is an excellent source of two omega-3 fatty acids: EPA (eicosopentanoic acid) and DHA (docosahexanoic acid) and can be obtained from a variety of fish such as: menhaden, sardine, anchovy, tuna etc. The nutritional literature is rich with data supporting the anti-inflammatory benefit of increasing omega-3 fatty acids in relationship to omega-6 fatty acids in the diet, especially in the case of surgical patients and/or those that are critically ill. (1-3)

Modulation of the Inflammatory Reponse

An increased level of omega-3 fatty acids in the diet leads to their increased incorporation and a corresponding decrease in the incorporation of omega-6 arachidonic acid into immune and other cell membrane phospholipids. Ultimately, this promotes a less inflammatory state. Figure 1 shows an overview of the cellular mechanisms by which omega-3 fatty acids help to decrease the inflammatory response to major surgery and critical illness.(2)

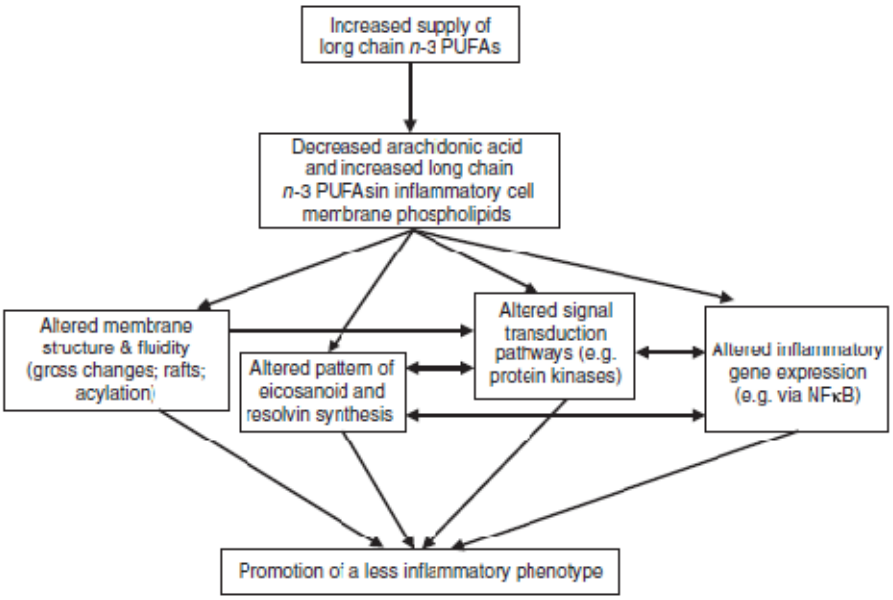

Fig. 1. Representation of the cellular mechanisms by which long chain n-3 PUFAs result in decreased inflammation.

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n6:n3 fatty acid ratio

The n6:n3 ratio refers to the quantity of n3 consumed in relation to the quantity of n6. Much has been written on the role of the ratio of n6:n3 fatty acids in health and chronic disease. From an evolutionary perspective, the diet is thought to have had a n6:n3 of 1:1 (4), however the typical western diet has a pro-inflammatory ratio of >15:1.(5) Based on the above, the ratio of n6:n3 fatty acids seems to effect the patient response to disease by favoring either a more inflammatory or less inflammatory pathway of eicosanoid production. In the surgical and critical care settings, it is important to modulate the inflammatory response to avoid excessive inflammation. The exact ratio that best modulates the inflammatory response has not been confirmed. The work from Morlion et al with IV lipids in post-operative trauma has suggested an n6:n3 ratio of 2:1.(6)

Safety

In its 2004 press release announcing the approval of a qualified health claim for reduced risk of coronary heart disease on conventional foods that contain EPA and DHA omega-3 fatty acids, the U.S. Food and Drug Administration (FDA) recommended that consumers not exceed more than a total of 3 g/d of EPA and DHA n3 fatty acids per day. (7) A slightly modified form of fish oil (ethyl esters providing 1.86 g EPA and 1.5 g DHA per day) has been approved by the FDA for treatment of hypertriglyceridemia. (8)

In its 2005 report on Dietary Reference Intakes (DRI) of macro-nutrients, the Institute of Medicine cited there was not enough data available to set an upper level of intake for EPA and DHA from fish oil. (9) The recommendations in the DRI reports are established for long term intake by the general healthy population. No attempt is made to recommend nutrient intakes for clinical applications to support the nutritional management of medical conditions.

A common concern among clinicians is that incorporation of EPA and DHA from fish oil into cell membranes may have antithrombotic properties and cause an increase in bleeding time. An increase in bleeding time may cause excessive blood loss and impair healing of wounds and surgical incisions. An overview of studies that tested the intake of fish oil on platelet aggregation and bleeding time is summarized below. Given that EPA and DHA content vary across fish oils, it's important to use the EPA and DHA content vs. total grams of fish oil when evaluating studies.

A 1993 study that examined bleeding time in n=16 surgical patients was done by Swails et al. (10). This report used IMPACT® Formula and patients received on average 1.5 g EPA and 0.5 g DHA per day for one week after surgery. The authors found no effect on platelet aggregation, but noted this finding was different than some of the other work from the 1980's done in small populations of healthy men (11,12). The proposed explanation was that these earlier studies provided EPA for a longer time period which allowed for a greater change in membrane characteristics. Of note, work done by Mu et al. showed incorporation of EPA and DHA into rat erythrocyte membranes increased in a linear fashion during each week of the three weeks of fish oil supplementation.(13)

The effect of supplemental α-linolenic acid (ALA) verses EPA and DHA in normal healthy adults was studied by Freese and Mutanen (14). Study subjects received 7.0 g of ALA or 5.6 g EPA and DHA per day for four weeks (values are supplemented and estimated dietary contribution). The level of fatty acids studied is higher than what would be expected to be consumed in a diet of healthy subjects. The results suggest that ALA from linseed oil and EPA and DHA from fish oil have similar effects on

bleeding time, fibrinogen, antithrombin III, factor VII coagulant activity, and plasminogen activator inhibitor-1 in healthy individuals.

Several studies have examined the effects of EPA and DHA in cardiovascular surgery. Leaf et al. (15) administered ethyl esters of EPA (4.1 g/d) and DHA (2.8 g/d) in capsules to coronary angioplasty patients two weeks before the procedure. Aspirin (325 mg/d) was included as part of normal care for all patients (n=447). As compared to the corn oil control group, there was no difference in bleeding time when evaluated on the day of the procedure and after three months of supplementation.

Harris (16) summarized the data from 19 clinical trials that used fish oil or enriched sources of EPA and DHA in coronary surgery patients. Most of the study subjects were also given aspirin or other anticoagulation therapy. Doses ranged from an EPA and DHA dose of 1.4 g/d to 6.9 g/d used by Leaf et al. (15). Duration of supplementation was as short as 28 d or as long as 28 months. Thirteen of the studies provided more than 3.0 grams per day of EPA and DHA. The following statement best summarizes the conclusion of this assessment:

> *"Thus, the experience has been virtually unanimous: omega-3 fatty acid supplements do not increase the risk for clinically significant bleeding, even in patients also being treated with antiplatelet or antithrombotic medications. Anecdotal reports of an increased bruising tendency have not been tested in a controlled setting, nor has the possible adverse interaction between omega-3 fatty acids and newer antiplatelet drugs (eg, clopidogrel) been examined directly."*

Summary

A number of studies have been completed that have studied the effect of fish oil and the n3 fatty acids in fish oil, EPA and DHA. Even with the co-administration of anti-coagulant compounds, the use of fish oil in doses beyond what is found in many enteral formulas has not been found to cause the bleeding time of patients to be extended beyond the normal range of healthy individuals. Nor did it produce any clinically significant bleeding events in these studies. As always, clinicians need to be aware of the amount of EPA and DHA administered and the time over which it is administered, and patients on anticoagulant therapy need to be monitored according to clinician orders.

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