Fish oil and its effects on inflammation in HIV-infected persons: A preliminary review

B Swanson1, JK Keithley1

Abstract

Introduction

The purposes of this review are to: a) provide an overview of fish oil and HIV-related inflammation, and b) examine the available evidence on the effects of fish oil to modulate parameters of inflammation in HIV-infected individuals.

Materials and methods

Combinations of search terms related to HIV infection, fish oil, omega-3 fatty acids, inflammation, and immunomodulation were used to search four electronic databases. Included studies: were primary research, were published in English in the past decade (2003-2013), sampled adult populations (≥18 years), included samples that were HIV-infected on antiretroviral therapy (ART) regimens with undetectable viral loads, tested fish oil interventions, and reported inflammatory outcomes. The search initially yielded twenty-three citations; two clinical trials met the inclusion criteria.

Results

Both trials tested similar fish oil supplements in doses of either 2 grams or 4 grams/day with an average study duration of 18 weeks and an average sample size of 43. In the study that tested a dose of 2 grams/day, soluble tumour necrosis factor-alpha receptor I (sTNFR-I) decreased significantly; in the study that tested a dose of 4 grams/day, there were significant increases in leukotriene B5 (LTB5) and leukotriene B5/leukotriene B4 (LTB5/LTB4) ratio. Neither study reported changes in high sensitivity C-reactive protein (hsCRP).

Conclusion

This preliminary evidence, although suggestive of effects for favourably modulating parameters of inflammation, is not sufficient to make fish oil recommendations for HIV-infected persons. Pending additional studies, clinicians should be guided by appropriate professional and governmental recommendations, and researchers should continue to examine this area more fully using well-designed studies, larger sample sizes and older populations, appropriate fish oil supplements and dosages, and a comprehensive array of inflammatory endpoints.

Introduction

Purpose

The introduction of highly active antiretroviral therapy (HAART) has increased the life span of persons who are HIV-infected (HIV+). However, the aging of the HIV+ population has led to increased incidence of age-related morbidities, such as non-AIDS malignancies and cardiovascular disease (CVD), that were rarely seen in the pre-HAART era. These comorbidities, known as inflammation, have been linked to persistent inflammation and elevated levels of soluble proinflammatory cytokines that are postulated to be maintained (a) by the constant antigen burden imposed by HIV and other chronic viral co-pathogens, such as cytomegalovirus (CMV), and (b) by HIV-induced disruption of intestinal epithelial integrity with subsequent translocation of gut microflora into the systemic circulation.

Fish oil may be an effective treatment option for reducing HIV-related inflammation. Cold water fish are rich in omega-3 fatty acids which have anti-inflammatory effects and have been shown to stimulate regeneration of damaged intestinal mucosa. In this review, we provide an overview of fish oil and HIV-related inflammation and examine the available evidence on the effects of fish oil to modulate parameters of inflammation in HIV-infected individuals.

Fish Oil

Omega-3 fatty acids, also known as n-3 fatty acids because they have a double bond at the third carbon (n-3), are highly unsaturated fatty acids (HUFAs). The three major types of omega-3 fatty acids are: a) alpha-linolenic acid (ALA), b) eicosapentaenoic acid (EPA), and c) docosahexaenoic acid (DHA). ALA is found primarily in vegetable oils such as flaxseed, canola, and soybean, and in nuts such as walnuts; EPA and DHA are found in fatty cold water fish such as salmon, sardines, tunas, herring, mackerel, and anchovies and, to a lesser extent, in shelfish such as oysters, crab, and shrimp (Table 1). Fish oil supplements are available in liquid, capsule, and tablet forms. Similar to other oils or fats, fish oil is rich in calories and provides 9 kcal/gram. A summary of fish oil safety considerations is presented in table 2.

HIV Infection and Inflammation

HIV infection is associated with chronic inflammation. Elevated levels of interleukin-1-beta (IL-1β), interleukin-6 (IL-6), gamma IFN (IFN-γ), and tumour necrosis factor-alpha (TNF-α) have been detected in the serum, cerebrospinal fluid, and cell culture supernatants of HIV-infected persons. Direct antigenic stimulation of immune cells secondary to sustained viral replication accounts for some, but not all, of the inflammation associated with HIV infection. Indirect mechanisms, such as activation of immune cells by HIV gene products, suboptimal immune

*Corresponding author
Email: barbara_a_swanson@rush.edu

1 Rush University College of Nursing, Chicago, Illinois, USA

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Table: 1 Table 1. Omega-3 Fatty Acids in Selected Fish and Shellfish*

<table>
<thead>
<tr>
<th>Omega-3s (per 100 grams edible portion)</th>
<th>EPA</th>
<th>DHA</th>
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<tbody>
<tr>
<td>Salmon</td>
<td>0.3-0.8</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>Sardines</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Tuna</td>
<td>0.3-0.4</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td>Herring</td>
<td>0.7-1.0</td>
<td>0.7-0.9</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.9-1.0</td>
<td>1.2-1.6</td>
</tr>
<tr>
<td>Anchovies</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Crab</td>
<td>0.2</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Oyster</td>
<td>0.2-0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Shrimp</td>
<td>0.2-0.3</td>
<td>0.1-0.2</td>
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</tbody>
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to predict mortality in HIV-infected persons.13

Omega-3 Fatty Acids and Inflammation
When consumed as fish or fish oil supplements, EPA and DHA replace arachidonic acid in cell membranes and inhibit the synthesis of proinflammatory arachidonic acid metabolites.14 A large body of literature has demonstrated that EPA and DHA reduce plasma concentrations of inflammatory cytokines.15 In clinical trials, fish oil supplementation has been associated with symptom relief and reductions in serum levels of proinflammatory cytokines in persons with rheumatoid arthritis and asthma,16,17 reduced plasma CRP and IL-6 levels in persons with pancreatitis,18 and reduced flares in persons with Crohn’s disease.19 Data on the effects of fish oil for managing HIV-related inflammation are limited. In a murine model of AIDS, mice fed a fish oil diet showed reductions in LPS-stimulated splenocyte production of TNF-α, leukotriene B4, and IL-1 compared to mice fed a corn oil diet.20 Limited human trials of fish oil to manage HIV-related triglyceridemia have found that it is generally well-tolerated and not associated with immunological or virological adverse events.21,22,23,24

Materials and methods
The question to be answered by the literature review was: What are the effects of fish oil on inflammatory parameters in HIV-infected persons? Four electronic databases—PubMed, Ovid-Medline, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and Cochrane Database of Systematic Reviews—were systematically searched. Search terms included HIV infection, fish oil, omega-3 fatty acids, inflammation, and immune. Reference lists from all retrieved articles also were searched for potentially relevant studies. All retrieved studies were independently screened and reviewed by two reviewers.

Effects of Inflammation on HIV Disease Progression & Mortality
HIV-related inflammation has serious implications for HIV disease progression.3 Proinflammatory cytokines (e.g., IL-1β, TNF-α) have been shown to upregulate HIV replication in cells at the entry and transcription steps of the viral lifecycle and induce apoptosis of activated CD4+ T lymphocytes.3 There is also evidence that proinflammatory cytokines have thymosuppressive effects and may reduce the regenerative capacity of the thymus to replace lost immune cells.12 In this state of immunodeficiency, latent co-pathogens, such as CMV and herpes zoster, can reactivate and further contribute to the cycle of immune activation, inflammation, and immunodeficiency.3 Given the deleterious effects of inflammation, it is not surprising that C-reactive protein (CRP) levels have been shown control of chronic viral infections (e.g., CMV, Epstein-Barr virus), and HIV-induced disruption of the gastrointestinal mucosa with subsequent bacterial translocation into the systemic circulation all contribute to chronic immune activation and release of proinflammatory cytokines.2 Several studies have shown that inflammation persists despite HAART-mediated viral suppression, possibly due to ongoing low level replication of HIV and co-pathogens.11

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The search was limited to studies: that were primary research; published in English in the past decade (2003-2013); that included adult populations (>18 years); that sampled HIV-infected persons who were on antiretroviral therapy (ART) regimens with undetectable or suppressed viral loads; that tested fish oil interventions; and that reported immune outcomes. The following characteristics were extracted from each of the retrieved studies: author and publication year; study design; sample size; fish oil intervention/dose; study duration or time period; immune markers studied; and findings (Table 3). Because of the limited number of studies retrieved, no statistical combining was done.

Results
The initial search of databases and relevant references yielded twenty-three citations. After screening, twenty-one did not meet inclusion criteria, leaving two remaining articles.25,26 Both studies used a placebo-controlled, double-blind, randomized trial (PCRT) design. One study was conducted in the United States25, and the other in Denmark.26 The sample sizes of the two studies were N=35 and N=51, respectively. For the fish oil intervention, both studies tested omega-3 acid ethyl esters, with a dose of either 2 grams or 4 grams/day and a study duration of either 24 or 12 weeks. The measured inflammatory markers were high sensitivity C-reactive protein (hsCRP); interleukin 6 (IL-6); soluble tumour necrosis factor-alpha receptor I (sTNFR-I); soluble tumour necrosis factor-alpha II (sTNFR-II); leukotriene B5 (LTB5); and leukotriene B4 (LTB4). In an all-male sample with moderate CVD risk, Hileman et al.25 reported a significant decrease in sTNFR-I, and no changes in hsCRP, IL-6, or sTNFR-II. Adherence was measured by pill counts, and the supplement was well-tolerated with no adverse events reported. In a sample of both males and females considered at risk for CVD because of ART, Thysgaard et al.26 reported a significant increase in LTB5 and LTB5/LTB4 ratio, and no changes in hsCRP. Compliance was determined by measuring EPA and DHA incorporation into neutrophils and, similar to the Hileman et al. study, the supplement was safe and well-tolerated.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Most recent clinical trials of omega-3 fatty acids in HIV-infected individuals have tested their lipid modulatory effects. Two meta-analyses of these trials concluded that treatment with omega-3 fatty acids using a range of doses was associated with reductions in triglyceride levels and no effects on selected immune parameters. Prior to the widespread use of antiretroviral therapy, several early studies examined the effects of fish oil supplementation on cytokine production in HIV-infected individuals. Although Bell et al.29 noted increased eicosanoid and cytokine production following 6 weeks of 2 gm of EPA+DHA/day, supplementation was accompanied by a downward trend in CD4+ T lymphocyte count. Hellerstein et al.30 reported no effect of 4.5 gm EPA+DHA/day on serum concentrations of TNF-α, IL-1β, or IFN-γ. Virgili et al.31 reported decreased IL-1β production following supplementation with 1.8 gm EPA+DHA/day for 6 weeks. In three other early studies,27,28,32,33,34,..

Table 2: Fish Oil Safety Considerations

<table>
<thead>
<tr>
<th>Description</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>In the U.S. fish oil has Generally Recognized As Safe (GRAS) status and is well-tolerated at doses of 3 grams/day or less.8</td>
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<tr>
<td>Individuals with fish or shellfish allergies also may be allergic to fish oil.</td>
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<tr>
<td>Fish oil supplements may extend bleeding time; therefore, concomitant use of drugs such as anticoagulants and non-steroidal anti-inflammatory drugs may be contraindicated.</td>
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</tr>
<tr>
<td>Fish oil is sometimes accompanied by minor gastrointestinal upset (e.g., belching, nausea, diarrhea) and is best tolerated when taken with meals.</td>
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<tr>
<td>The American Heart Association recommends consuming at least one serving of fish (e.g., 3.5 oz. cooked, ¼ cup flaked) twice weekly. In people with documented coronary heart disease (CHD), 1 gram of EPA+DHA daily is recommended, preferably from fatty fish.9</td>
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<tr>
<td>According to the Institute of Medicine Dietary Reference Intakes (DRIs), the Adequate Intakes (AIs) of omega-3 fatty acids are 1.6 g/day for adult men and 1.1 g/day for adult women.10</td>
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the investigators reported that fish oil supplementation had no adverse effects on either CD4+ T lymphocyte count or cytokine production.

In the last decade, only two PCRTs have studied the effects of fish oil supplements on a slightly broader array of inflammatory parameters in HIV-infected persons on stable ART. Both studies, focused primarily on CVD risk, had relatively small sample sizes (N=35 or N=51) and an average study duration of 18 weeks. The fish oil supplements in both studies were similar except for the dosage, which was either 2 grams/day or 4 grams/day.

Inflammatory outcomes were limited to measures of sTNFR-I, sTNFR-II, hsCRP, IL-6, and LTB5. In the Hileman et al. study, a significant reduction was found for sTNFR-I, while in the Thusgaard et al. study, significant increases were found for LTB5 and LTB5/LTB4 ratio. sTNFR-I & II, induced by TNF-α and characterized by longer half-lives than their ligand, have been shown to be reliable markers of plasma concentrations of TNF-α over time. LTB4 is an arachidonic acid metabolite that has greater proinflammatory activity than LBT5 which is derived from EPA. While these inflammatory parameters were favourably modulated with fish oil supplementation, other inflammatory parameters did not significantly change. Since 3g/day is the dose recommended by the American Heart Association (AHA), it is possible that the doses were too low to see effects for other inflammatory parameters. Measuring other markers that may be more sensitive to anti-inflammatory agents, such as intracellular cytokine concentrations, will help elucidate the effects of fish oil for reducing HIV-related inflammation.

**Conclusion**

Research on the effects of fish oil on HIV-related inflammation remains in a nascent state. Although several studies have examined the effects of fish oil on specific diseases in HIV-infected persons—primarily dyslipidemia—only two recent clinical trials have examined its effects on inflammatory parameters. Given the paucity of current evidence, it is premature to advance specific fish oil recommendations for HIV-infected individuals. Until additional studies can be conducted, clinicians should follow accepted fish oil guidelines as recommended by appropriate governmental and professional organizations.

To facilitate future research, investigators should undertake well-designed clinical trials, use power analysis to guide sample size and include older populations, compare fish oil supplements that are of similar composition and sufficient dosage, incorporate biological markers of incorporation of omega-3 fatty acids into cell membranes to evaluate adherence, and include a comprehensive array of inflammatory parameters.
endpoints, such as intracellular and inducible cytokine concentrations. It is from such studies that we will most likely identify those individuals who might best benefit from fish oil supplementation.

References